Clinical Study

LH Dynamics in Overweight Girls with Premature Adrenarche and Slowly Progressive Sexual Precocity

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Background. Excess adiposity and premature adrenarche (PA) are risk factors for the development of polycystic ovary syndrome (PCOS). *Methods*. Girls with slowly progressive precocious breast development, who were overweight and had PA (SPPOPA, 6.2–8.2 years, $n = 5$), overweight PA (6.6–10.8 years, $n = 7$), and overweight premenarcheal controls (OW-PUB, 10.6–12.8 years, $n = 8$) underwent hormonal sleep testing and GnRH agonist (GnRHag) and ACTH tests. *Results*. Despite an insignificant sleep-related increase in LH and prepubertal baseline hormone levels, SPPOPA peak LH and estradiol responses to GnRHag were intermediate between those of PA and OW-PUB, the LH being significantly different from both. *Conclusions*. GnRHag tests indicate that SPPOPA is a slowly progressive form of true puberty with blunted LH dynamics. These results argue against the prepubertal hyperandrogenism of excess adiposity or PA enhancing LH secretion or causing ovarian hyperandrogenism prior to menarche. Excess adiposity may contribute to both the early onset and slow progression of puberty.

1. Introduction

We have characterized a variant group of sexually precocious girls who presented diagnostic challenges that provided an opportunity to test hypotheses about pubertal pathophysiology. They met current criteria for sexual precocity, with breast and pubic hair development before 8 years of age [1–3]. However, they differed from girls with typical central precocious puberty (also termed complete, true, or gonadotropin-dependent premature puberty) because they had slowly progressive precocious breast development [4–6], were overweight, and had premature adrenarche (SPPOPA). Their early morning LH serum levels were also persistently prepubertal during the initial observation period. About one-third of girls with central precocity are overweight [7], about half have premature adrenarche (PA) [6], although it causes pseudoprecocity independently of true puberty [8], and only about 10% have early morning LH levels in the prepubertal range [9]. Thus, our SPPOPA group presented an uncommon, but not rare, combination of findings.

Their peripubertal adiposity and hyperandrogenism suggested that they were at risk of developing polycystic ovary syndrome (PCOS), a hyperandrogenic anovulation disorder that is often accompanied by obesity [10]. Obesity potentially predisposes to the development of PCOS by causing premenarcheal LH excess that is mediated by peripubertal hyperandrogenemia [11–13]. PA, a mild form of adrenal hyperandrogenism, potentially poses increased risk for the development of PCOS, particularly in obese and African-American or Hispanic girls [10, 14, 15].

The diagnostic challenge was to determine whether SPPOPA girls had early activation of the neuroendocrine-gonadal axis that ordinary testing failed to capture, whether their thelarche was due to adiposity-related peripheral estrogen formation [16], or whether they simply had pseudothelarche due to adipomastia. If they had adipomastia or estrogen excess of peripheral origin, one would expect LH dynamics to be suppressed, that is, no greater than the prepubertal pattern expected in isolated PA. If they had central precocity related to PA predisposing to PCOS, it might be expected that their LH would be higher than that of controls in a similarly early stage of puberty because of peripubertal hyperandrogenemia [11–13]; it might also be expected that inherent ovarian dysfunction would be apparent in early

puberty [17]. Thus, definition of their pathophysiology was potentially instructive for understanding the developmental origins of PCOS [10, 18]. To test these possibilities, we surveyed their hypothalamic-pituitary-ovarian function by analyzing gonadotropin secretion during sleep, since the first hormonal changes of puberty begin then [19]; by assessing their gonadotropin and sex steroid responses to a GnRH agonist (GnRHag) test; and by testing their adrenal androgenic sensitivity to ACTH. The results indicate that these girls indeed have a slowly progressive form of central precocious puberty, with blunting of their early pubertal LH production in spite of peripubertal hyperandrogenemia; these results may be related to our recent findings in healthy girls that excess adiposity subtly blunts gonadotropin secretion during the early stages of puberty [20].

2. Subjects and Methods

2.1. Subjects. SPPOPA girls (4 African-American, 1 Hispanic) presented with premature breast and pubic hair development; thelarche had occurred at 5–7.5 years of age, was predominantly at stage 3 at admission, and was uniformly preceded by pubarche, by a median of 0.5 years. Preadmission early morning blood sampling showed that these girls' premature pubarche was accompanied by adrenarcheal levels of dehydroepiandrosterone sulfate (DHEAS) and testosterone; however, despite their obvious thelarche, they had prepubertal gonadotropin and estradiol levels. PA girls (3 African-American, 4 Caucasian) presented with pubarche that began at 3–8 years of age, and 6/7 had above average height velocity, high bone age/height age ratio, obesity, acanthosis nigricans, or high DHEAS for pubic hair stage, which are sometimes considered to be signs of "exaggerated adrenarche" [10, 21, 22], but none had breast development. Healthy overweight pubertal (OW-PUB, 7 African-American, 1 Hispanic) female volunteers were recruited by advertisement and were premenarcheal and predominantly breast stage 3, as previously described [20]. For the purposes of this study "overweight" was used in the sense of "excessive" and defined as body mass index (BMI) >85th percentile and, thus, included obese subjects (≥95th percentile) [23]. Patients were followed for 0.4 years or more (median 2.0 ± 0.5). Congenital adrenal hyperplasia was excluded from all by ACTH-testing (see below). These studies were approved by the University of Chicago Institutional Review Board and were performed after obtaining assent of the girls and consent of the parents.

2.2. Study Protocol. Subjects were admitted to the University of Chicago General Clinical Research Center between 2001 and 2005 and studied by a previously reported protocol (Table 1) [20]. At 1900 hr, a hormonal sleep test was begun with sampling by continuous blood withdrawal until 2 or more hr after sleep onset, as assessed by observation, with the exception of 3 subjects in the PA group and 1 in the SPPOPA group whose sleep studies lasted 0.3–1.3 hr. LH was measured every 20 min, FSH and estradiol in 2-hr pools. At 0800 hr the next morning, baseline fasting

blood samples were obtained. An oral glucose tolerance test was then performed according to American Diabetes Association guidelines: after a fasting sample was obtained, subjects were given glucose in solution (Glucola), 1.75 grams per kg body weight up to a maximum of 75 grams, with repeat sampling at 2 hours for serum glucose and insulin. Concurrently, blood was sampled every 15 min to determine baseline mean gonadotropin levels. Then a pelvic ultrasound examination was performed. At 1200 hr, low-dose dexamethasone ($0.25 \, \text{mg/m}^2$) was given orally to attenuate spontaneous adrenocortical secretion during the subsequent ACTH test. At 1600 hr, basal sampling was performed, then low-dose ACTH1-24 ($1.0 \, \text{mcg/1.7 m}^2$ IV) was administered, and blood was sampled at 15, 30, and 60 min for steroids. At 1800 hr, GnRHag (leuprolide acetate) (10 mcg/kg SC) was given, after collecting blood every 15 min for 1 hr for basal gonadotropins, and gonadotropins were sampled for 4.0 hr. Post-GnRHag steroidogenic responses were assessed at 18 hr, then dexamethasone was readministered and steroids further assessed at 20–24 hr (1400–1800 hr).

2.3. Laboratory and Procedural Methods. As previously reported, serum LH and FSH were measured by immuno-fluorometric assays (Delphia, Wallach, Finland); total testosterone and cortisol by Diagnostic Products Corporation radioimmunoassay kits (Los Angeles, CA); dehydroepiandrosterone sulfate (DHEAS) by Diagnostic Systems Laboratory kits (Webster, TX); estradiol by Pantex immunoassay kit (Santa Monica, CA); free testosterone and sex hormone binding globulin binding capacity were calculated from a competitive protein binding assay [20]. Postchromatographic radioimmunoassays were used for steroid intermediates (17-hydroxyprogesterone, androstenedione, 11-deoxycortisol, 17-hydroxypregnenolone, and DHEA). Serum insulin was initially assayed by a double-antibody RIA; the method was changed to Immulite assay in 2004, and the data are expressed in terms of the latter assay [24]. Each hormone on a study subject was assayed simultaneously. Values below the limits of assay sensitivity were set to this limit for statistical analysis, as previously reported. Plasma glucose was measured using a glucose analyzer (YSI Model 2300 STAT; Yellow Springs Instruments, Yellow Springs, OH). Insulin resistance was approximated by homeostatic model assessment (HOMA) according to the equation HOMA = [fasting plasma insulin (mU/L) × fasting plasma glucose (mmol/L)]/22.5 [25]. Real-time pelvic ultrasound imaging was performed in the Pediatric Radiology Department by the abdominal route using an Acuson Sequoia with a 4 Mhz transducer (Acuson, Mountainview, CA) according to the manufacturer's specifications using standard algorithms and a phantom probe for periodic calibration [26]. There was no significant variation between readings by the two radiologists who performed these studies. Ovarian volume was calculated according to the formula for ellipsoid bodies. Bone age was determined by a modification of the Greulich-Pyle method [27], and adult height was predicted by the Bayley-Pinneau method [28]. BMI percentiles were obtained from a national database [29] and height velocity norms from Tanner and Davies [30].

Table 1: Outline of study protocol.

Day	Clocktime	Procedure
Day 1	1900	Overnight hormonal sleep test
Day 2	0800	Baseline sampling begins
		Oral glucose tolerance test
		Pelvic ultrasound examination
	1200	Dexamethasone 0.25 mg/m^2 PO
	1600	Basal sample for steroids
	1601	ACTH1-24 (1.0 mcg/m^2 IV) test begins
	1700	Basal GnRHag test LH&FSH sampling begins
	1800	GnRHag test (leuprolide 10 mcg/m^2 SC) test begins
Day 3	1200	Post-GnRHag 18 hr sampling
	1201	Dexamethasone 0.25 mg/m^2 PO
	1400	Post-GnRHag sampling resumes (20 hr)
	1800	GnRHag test sampling ends (24 hr)

2.4. Data Analyses. Group data, including hormonal responses log-transformed as necessary for data normalization, were compared by one-way ANOVA (comparisons among groups) with subsequent pairwise comparisons performed by Tukey's method (sleep tests) or paired and unpaired Student's *t*-tests (baseline hormones), Fisher's exact test (for categorical variables), two-way repeated measures ANOVA (GnRHag test), and paired and unpaired Student's *t*-tests (2-sample comparisons). Primary outcome variables were the comparisons of SPPOPA to PA and to OW-PUB for sleep and GnRHag tests. Correction for multiple comparisons was carried out by Fisher's protected least significant differences post hoc testing. Results are expressed as mean ± SEM, unless otherwise stated. Two-tailed *P*-values < .05 were considered significant.

3. Results

3.1. Clinical Characteristics. Baseline BMI percentile and pubic hair stage were similar in the three study groups; SPPOPA and OW-PUB girls had similar breast stage and bone age (Table 2). Height velocities of all patients at entry were above average for age. SPPOPA breast development progressed slowly (averaging one stage yearly), and the bone age/height age ratio (1.12 ± 0.05) and predicted adult height (160.4 ± 2.7 cm) did not change significantly during untreated follow-up. Menarche was later documented at 9.4 and 10.5 years in two SPPOPA girls, which was at most mildly earlier than the 5th percentile for OW girls (10.1 yr, 95% confidence interval 9.5–10.7 yr) [2, 3], at normal heights of 159.1 and 152.9 cm, respectively. Neither of these girls had a remarkable premenarcheal hormonal pattern nor an elevated perimenarcheal free testosterone level. In two PA girls, menarche was later documented at 11.1 and 13.9 years of age at heights of 148.1 and 156.7 cm, respectively. In the latter, free testosterone levels were found to be high (15 pg/mL) shortly after menarche, BMI was 93rd percentile. Her course was remarkable for her mother having a history of PCOS, and over the subsequent year, she developed persistent hyperandrogenemia, acne, and irregular cycles, indicating that she had developed PCOS [31].

SPPOPA HOMA index was intermediate between PA and OW-PUB (Table 2), with one subject having insulin resistance (HOMA 10.8) in association with impaired glucose tolerance. However, impaired glucose tolerance prevalence was not significantly different among groups.

Early morning baseline hormone testing (Table 3) showed that all groups had similarly adrenarcheal DHEAS, androstenedione, and free testosterone levels, while SPPOPA and PA both had similarly prepubertal gonadotropin levels that differed significantly from those of OW-PUB girls. However, SPPOPA had baseline ovarian volume (Table 2) and estradiol levels (Table 3) intermediate between PA and OW-PUB. Baseline sex hormone binding globulin, 17-hydroxyprogesterone, and progesterone levels were similar among groups.

3.2. Sleep Test. SPPOPA resembled PA in having prepubertal evening wake LH and FSH levels, which were significantly lower than in OW-PUB (Table 4). Wake estradiol levels of two SPPOPA girls exceeded the prepubertal range, so the mean for SPPOPA girls was intermediate between PA and OW-PUB girls, who differed significantly.

Peak sleep LH and estradiol of all but one SPPOPA and one PA girl were in the prepubertal range, as were all their FSH peaks (Table 4). The peak sleep LH of PA and OW-PUB girls differed significantly, and that of SPPOPA was intermediate. None of the groups had a significant sleep-related LH rise: mean sleep LH in PA was 0.13 ± 0.1, in SPPOPA 0.15 ± 0.07 and in OW-PUB 0.68 ± 0.35 U/L. Sleep estradiol levels of both SPPOPA and PA were significantly lower than in OW-PUB (Table 4).

3.3. GnRHag Test. Despite their prepubertal gonadotropin levels at baseline and asleep, SPPOPA girls had LH responses to GnRHag testing that were both significantly greater than those of PA girls and less than those of OW-PUB girls by

TABLE 2: Study group baseline clinical characteristics. Observed range for each study group is shown, as is 5th–95th percentile reference range of healthy prepubertal volunteers [20].

GROUP	AGE (yr)	BA (yr)	HA (yr)	HV[a] (cm/yr)	BMI %ile	Breast (Tanner)	Pubic Hair (Tanner)	Max Ov (cc)	Max Foll (#)	HOMA
PA (n = 7)										
Mean	8.1[b]	9.5[b]	9.0[c]	7.2	90	1.0[c,d]	3	2.2[c]	3.9	2.6[c]
SEM	0.5	0.5	0.5	2.4	6			0.6	1.4	0.3
Range	6.6–10.8	7.3–10.8	7.2–11.2	5.5–12.0	52–99	1	2-3	0.5–5.3	0–10	1.4–3.8
SPPOPA (n = 5)										
Mean	7.5[b]	9.9	9.0[c]	7.4	97	2.7	3	3.8	6.0	4.6
SEM	0.4	0.5	0.7	0.8	2			0.3	1.2	1.3
Range	6.2–8.2	8.8–11.5	7.0–11.0	5.8–10.1	91–99.9	2-3	3-4	2.7–4.5	4–8	1.9–10.8
OW-PUB (n = 8)										
Mean	11.3	11.5	12.0	—	95	3.1	3	5.9	6.0	5.2
SEM	0.3	0.6	0.5	—	2			1.6	1.4	0.7
Range	10.6–12.8	8.8–13.0	10.3–14.4	5.8–9.8[e]	86–99	3-4	2-4	1.8–10.7	0–10	3.0–9.0
Prepubertal (n = 20)										
Reference Range	*6.5–9.5*	*5.9–9.3*	*6.3–10.8*	*4.2–7.5* [e]	*11–99*	*1*	*1*	*0.7–5.6*	*0–10*	*0.79–8.7*

[a] Median.
[b] P versus OW-PUB < .05.
[c] P versus OW-PUB < .01.
[d] P versus SPPOPA < .01.
[e] Prepubertal range is 3rd–97th percentile for 7.5-year-old girls; pubertal range is 3rd–97th percentile for 11-year-old girls. From Tanner and Davies 1985 [30].
HA (height age); HV (height velocity); Max Ov (largest ovary); Max Foll (greatest number of follicles in maximum plane).

Table 3: Study group baseline pubertal hormone levels. Observed range for each study group is shown, as is 5th–95th percentile reference range of healthy prepubertal volunteers [20].

GROUP	LH (IU/L)	FSH (IU/L)	E2 (pg/mL)	Total T (ng/dL)	Free T (pg/mL)	SHBG (nM)	A'dione (ng/dL)	17OHP (ng/dL)	PROG (ng/dL)	DHEAS (µg/dL)
PA ($n = 7$)										
Mean	0.15[a]	1.7[a]	6.4[a]	15.6[a]	3.7	23	42.0	35.9	25.0	67
SEM	0.00	0.2	0.4	2.5	0.6	6.1	7.9	5.4	0.0	12
Range	≤0.15	0.9–2.8	<5.0–8.0	<10–26	≤2.0–6.0	8–54	<25–80	<25–64	<25	28–103
SPPOPA ($n = 5$)										
Mean	0.15[a]	1.6[a]	9.6	16.2	4.8	17	45.2	26.2	25.3	62
SEM	0.00	0.5	2.5	2.5	1.2	3.9	3.9	1.2	0.3	10
Range	≤0.15	0.9–2.9	<5.0–19	<10–21	≤2.0–8.0	2–23	36–59	<25–31	<25–26	35–87
OW-PUB ($n = 8$)										
Mean	2.1	3.7	24.8	27.4	6.6	24	74.1	48.4	25.4	40
SEM	0.71	0.8	6.5	4.5	1.1	3.2	15.2	8.8	0.4	7.4
Range	≤0.15–5.8	0.5–6.2	<5.0–53	14–47	4–10	9–40	29–149	<25–91	<25–28	11–72
Prepubertal ($n = 20$)										
Reference Range	*≤0.15*	*0.4–2.4*	*<5.0–8.0*	*≤10*	*≤2.0*	*16–58*	*<25–43*	*<25–52*	*<25*	*<5–42*

P-values versus OW-PUB; [a] $P < .05$.
E2 (estradiol); T (testosterone); SHBG (sex hormone binding globulin); A'dione (androstenedione); 17OHP (17-hydroxyprogesterone); PROG (progesterone); DHEAS (dehydroepiandrosterone sulfate).
Conversions to SI units: $E2 \times 3.61 = pmol/L$; Testosterone $\times 0.0347 = nmol/L$; A'dione $\times 0.0349 = nmol/L$; 17OHP $\times 0.0303 = nmol/L$; PROG $\times 0.318 = nmol/L$; Free testosterone $\times 3.47 = pmol/L$; DHEAS $\times 0.0271 = \mu mol/L$.

TABLE 4: Study group wake and sleep gonadotropin and estradiol levels. Observed range for each study group is shown, as is 5th–95th percentile reference range of healthy prepubertal volunteers [20].

GROUP	LH (U/L)		FSH (U/L)		Estradiol (pg/mL)	
	Mean Wake	Peak Sleep	Mean Wake	Peak Sleep	Mean Wake	Peak Sleep
PA ($n = 7$)						
Mean	0.16[a]	0.50[a]	1.3[a]	2.1	7.6[a]	5.5[a]
SEM	0.01	0.22	0.13	0.56	0.88	0.5
Range	≤0.15–0.20	≤0.15–1.8	0.85–1.7	1.0–5.2	≤5.0–10.5	≤5.0–8.0
SPPOPA ($n = 5$)						
Mean	0.15[a]	0.68	1.4[a]	2.0	13.1	7.9[a]
SEM	0.00	0.17	0.20	0.41	3.1	1.3
Range	≤0.15–0.17	≤0.15–1.2	0.72–1.9	1.1–3.0	5.5–23.0	≤5.0–12.0
OW-PUB ($n = 8$)						
Mean	2.6	5.3	4.0	4.4	25.5	28.9
SEM	0.89	1.7	0.87	0.88	4.4	7.2
Range	≤0.15–6.9	≤0.15–13.5	0.68–7.2	0.60–6.8	10.5–43.7	7.0–63.0
Prepubertal ($n = 20$)						
Reference Range	*≤0.15*	*0.15–0.85*	*0.40–1.6*	*0.5–3.0*	*≤5.0–16.0*	*≤5.0–9.0*

P-values versus OW-PUB: [a] <.05, [b] <.01.

ANOVA (Figure 1, Table 5). Their LH peaks were likewise significantly different ($P < .05$); that of PA was 3.1 ± 0.8, SPPOPA 10.0 ± 2.9, and OW-PUB 54.2 ± 14.6 U/L. The LH response at 4 hr was the best discriminant among groups; that of each SPPOPA case was >4.0 IU/L, which is the 90th percentile for prepubertal controls, in whom the only higher values occurred in ≥8.4 year-olds. In contrast, SPPOPA and PA had similar FSH responses to GnRHag that differed significantly from OW-PUB in being less-sustained. The LH/FSH ratio in response to GnRHag rose >1.0 in only 20% of SPPOPA, compared to 75% of OW-PUB, but in 60% it was above that of PA girls.

SPPOPA estradiol responses were intermediate between those of PA and OW-PUB girls, which differed significantly (Figure 1). The modal time of estradiol peak responses was not significantly different among groups but tended to be earliest within the 18–24 hr period in the PA group and latest within the OW-PUB group. SPPOPA estradiol peak responses (56.1 ± 13.2 pg/mL) occurred 18–22 hr post-GnRHag and were between those of PA (33.0 ± 5.8 pg/mL) and those of OW-PUB (148 ± 36 pg/mL), which differed significantly (Table 5).

SPPOPA and PA had similar 17-hydroxyprogesterone responses to GnRHag, and both were significantly less than those of OW-PUB (Table 5). The SPPOPA post-GnRHag testosterone 22-hr level was pubertal, significantly greater than that of PA, while that of androstenedione was intermediate between PA and OW-PUB, which differed significantly. The responses of progesterone and DHEA to GnRHag did not differ among groups.

3.4. ACTH Test. SPPOPA and PA had similarly adrenarcheal responses to ACTH that were elevated for age and similar to those of OW-PUB, though on average above them (Figure 2). Steroidogenic response peaks occurred within 30 minutes and were otherwise unremarkable.

4. Discussion

SPPOPA girls present an infrequent, but not rare, diagnostic challenge. The clinical presentation with premature breast and pubic hair development and course of these cases was typical of the slowly progressive form of central precocity [4, 5]. However, while early morning hormone sampling in these SPPOPA girls showed premature adrenarche, it did not show pubertal gonadotropin levels. Two mechanisms were considered as possibly underlying this clinical picture, aside from the possibility of the pseudothelarche of obesity. The first was that outpatient testing failed to detect early puberty, the alternate was that the combination of premature adrenarche and excessive adiposity caused premature thelarche via the enhanced peripheral estrogen formation of obesity. We also tested the hypotheses that if they were indeed pubertal, their peripubertal hyperandrogenism would predispose to increased LH levels as an early manifestation of PCOS [11–13] and premature adrenarche would predispose them to a unique ovarian androgenic response to GnRHag [17].

Consistent with the first mechanistic possibility, SPPOPA girls had responses to GnRHag testing that were significantly greater than those of PA girls, and thus had undergone pubertal gonadotrope activation. While diagnostic criteria for this test are not well established, their LH levels 4 hr post-GnRHag were all >4.0 U/L, which is in the midst of ranges of cut-offs proposed for diverse assays in diagnosing central precocity by GnRH testing (3.3–5.0 U/L) [1].

Adrenal androgen baseline levels and responses to ACTH of the SPPOPA and PA girls were elevated for age and tended to be higher than those of premenarcheal pubertal volunteers. SPPOPA girls did not have higher LH parameters than comparably overweight early pubertal controls, as might be expected if the hypothesis were true that peripubertal hyperandrogenism predisposes to elevated LH secretion of PCOS commencing during stage 3 of puberty

TABLE 5: Hormonal responses to GnRHag postdexamethasone. Post-GnRHag gonadotropin levels are shown at 4 hr and steroid levels at 22 hr. Mean ± SEM (observed range).

	Premature Adrenarche		SPPOPA		OW-PUB		PRE Reference Range [20]	
	Basal	Post-GnRHag	Basal	Post-GnRHag	Basal	Post-GnRHag	Basal	Post-GnRHag
LH (U/L)	0.15 ± 0.8[a] (≤0.15)	3.1 ± 0.8[b,c] (0.8–5.9)	0.15 ± 0.0[a] (≤0.15)	9.8 ± 2.7[a] (4.3–19)	2.0 ± 1.0 (0.2–8.2)	38 ± 8.5 (4.8–76)	<0.15	1.0–7.0
FSH (U/L)	1.4 ± 0.2 (0.9–2.2)	21.4 ± 3.9 (9.1–42)	1.1 ± 0.2[a] (0.6–1.8)	26.4 ± 7.3 (23–52)	3.1 ± 0.7 (0.5–6.1)	24.9 ± 2.7 (16.5–32)	0.4–1.7	7.9–32
LH/FSH (Ratio)	0.12 ± 0.01[a] (0.07–0.17)	0.16 ± 0.04[a] (0.05–0.31)	0.16 ± 0.03 (0.08–0.25)	0.53 ± 0.23 (0.10–1.4)	0.46 ± 0.18 (0.09–1.6)	1.7 ± 0.50 (0.15–4.5)	0.09–0.43	0.04–0.28
E2 (pg/mL)	6.0 ± 1.8[a] (≤5.0–10)	25.8 ± 3.2[a] (16–39)	6.5 ± 0.5[a] (≤5.0–8.0)	52.8 ± 13.1 (19–95)	19.0 ± 4.5 (≤5.0–39)	134 ± 34.1 (23–298)	≤5.0–7.0	7.0–49
PROG (ng/dl)	≤25 ± 0.0 (≤25)	≤25 ± 0.0 (≤25)	≤25 ± 0.0 (≤25)	≤25 ± 0.0 (≤25)	≤25 ± 0.0 (≤25)	29.8 ± 2.6 (25–44)	≤25	≤25
17OHP (ng/dl)	≤25 ± 0.0 (≤25)	≤25 ± 0.0[a] (≤25)	≤25 ± 0.0 (≤25)	25.8 ± 0.4[a] (≤25–27)	≤25 ± 0.0 (≤25)	73.0 ± 18.2 (25–172)	≤25	≤25
DHEA (ng/dl)	121 ± 20.3 (67–212)	98.2 ± 9.5 (77–129)	105 ± 21 (50–162)	80.8 ± 9.9 (42–96)	92.5 ± 17.6 (41–158)	89.6 ± 10.6 (44–125)	28–59	27–69
A'dione (ng/dl)	30.1 ± 3.8 (≤25–52)	28.0 ± 1.6[a] (25–35)	28.4 ± 3.4 (≤25–42)	37.9 ± 8.9 (25–72)	43.9 ± 7.9 (25–88)	76.6 ± 17.4 (25–169)	≤25	25–40
Total T (ng/dl)	≤10 ± 0.0 (≤10)	≤10 ± 0.0[a,c] (≤10)	12.2 ± 2.3 (10–19)	11.5 ± 0.6 (10–13)	15.2 ± 2.4 (10–30)	18.3 ± 3.5 (10–40)	≤10	≤10
Cortisol (µg/dl)	2.0 ± 0.3 (1.0–3.0)	1.6 ± 0.2 (1.0–2.0)	2.0 ± 0.3 (1.0–3.0)	1.5 ± 0.3 (0.9–2.0)	2.0 ± 0.6 (0.9–2.0)	1.5 ± 0.3 (0.9–3.0)	1.0–3.0	1.0–5.0

[a] P versus OW-PUB <.05.
[b] P versus OW-PUB <.01.
[c] P versus SPPOPA <.05.
Conversions to SI units: DHEA × 0.0347 = nmol/L; for all other conversions, refer to Table 2.
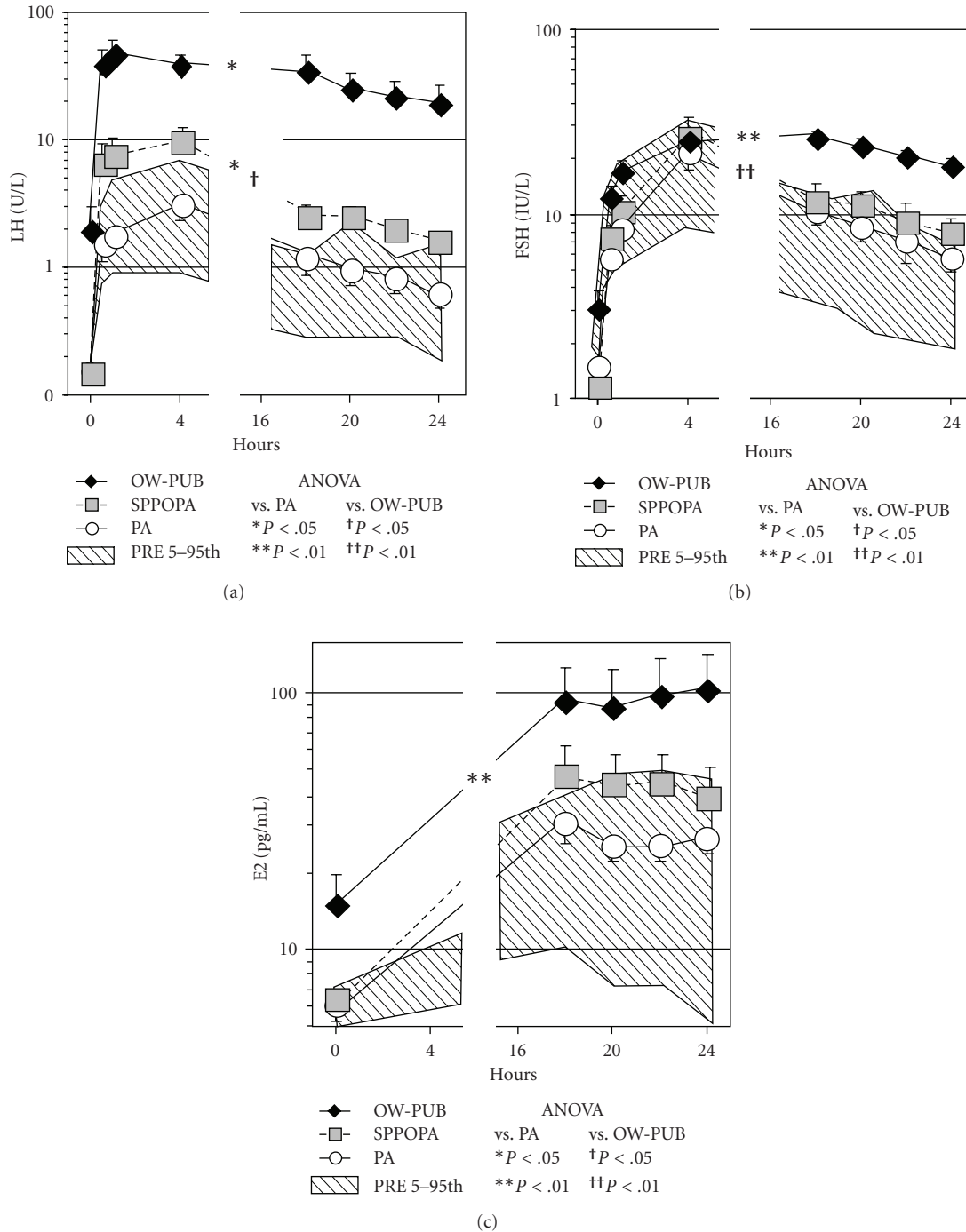
(a)

(b)

(c)

FIGURE 1: Baseline and peak LH, FSH, and estradiol (E2) responses to GnRHag testing. SPPOPA girls had greater LH responses to GnRHag testing than PA girls and FSH and E2 responses intermediate between those of PA and OW-PUB girls. Prepubertal (PRE) reference range shown for comparison [20]. Note logarithmic axes. Error bars depict SEM.

[11–13]. Indeed, LH was lower, as discussed below. However, our SPPOPA group was not hyperandrogenic for their stage of pubertal maturation, so it remains unclear at what point in pubertal development, and at what level, hyperandrogenemia becomes capable of stimulating pulsatile LH secretion, as it does after menarche [32, 33]. Additionally, SPPOPA girls had no evidence of the pubertal ovarian

DHEA hyperresponsiveness that has been reported to follow presentation with PA and has been suspected of indicating risk for developing PCOS [17]; the difference in findings may be explicable by the difference in BMI status of our PA population or our study design in which low-dose dexamethasone was used to eliminate artifacts arising from coincidental adrenal secretion. However, our limited long-term follow-up
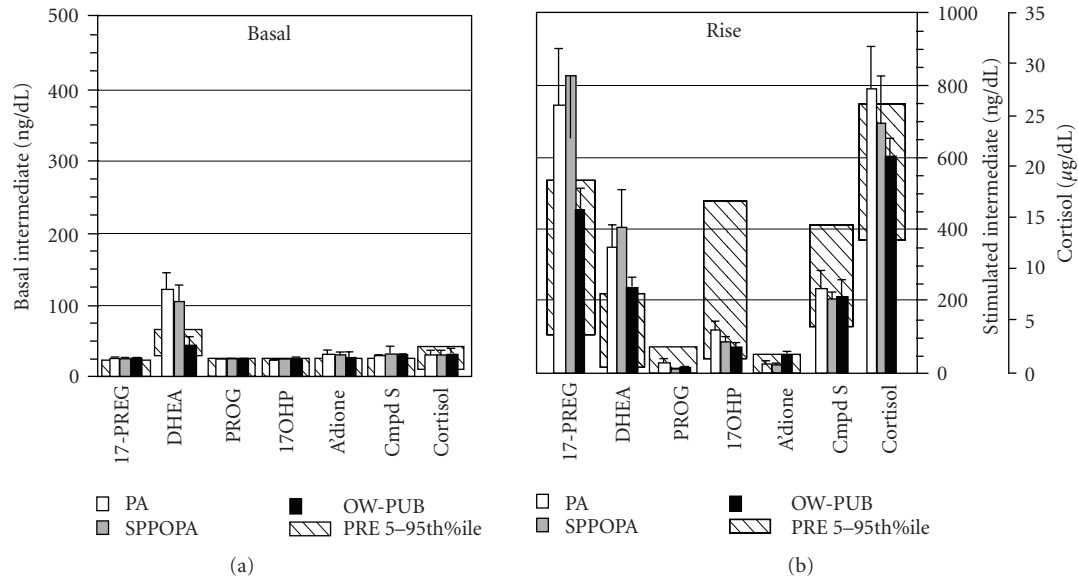
Figure 2: Steroid intermediate basal levels and responses to ACTH-stimulation. Although SPPOPA and PA girls had DHEA basal levels and responses and 17-hydroxypregneneolone responses elevated for age, the three groups did not differ in their basal levels or adrenal responses to ACTH. Prepubertal (PRE) reference range shown for comparison [20]. Note different scales for basal and stimulated steroid intermediates. Error bars depict SEM. Abbreviations not otherwise used: 17-PREG (17-hydroxypregnenolone); Cmpd S (11-deoxycortisol).

revealed one PA girl to develop PCOS after menarche; there was nothing in her study that distinguished her from the others in the PA group except the maternal history of PCOS.

The slowly progressive form of central precocious puberty generally differs from classical (rapidly progressive) central precocity in its lesser activation of hypothalamic GnRH secretion [34]. Thus, these patients ordinarily have lower LH peaks and LH/FSH ratios in response to GnRH [6, 34, 35], fewer and lower LH pulses during sleep [6], and tend to be less estrogenized [5, 35]. Clinically, pubertal tempo is not accelerated [4, 5], the age of menarche is, on average, within normal limits [6, 35], and adult height potential is preserved without treatment [35].

Although the SPPOPA group was typical of slowly progressive precocity in these general ways, their LH dynamics were significantly attenuated for their level of pubertal maturation in comparison to ordinary OW early pubertal controls. Wake gonadotropins and LH responses to GnRHag were significantly lower than those of the comparably overweight pubertal controls. These overweight controls themselves had a blunted sleep-related rise in LH pulse amplitude and pulse frequency relative to normal-BMI controls; however, they had responses to GnRHag like those of normal-weight pubertal girls [20]. The data are compatible with the possibility that early pubertal girls are particularly sensitive to the gonadotropin-suppressive effects of obesity.

Evidence is accumulating that excess adiposity reduces LH production. LH levels and pulse amplitude are low in morbidly obese men with hypogonadism [36] and low in eumenorrheic obese women with anovulatory cycles [37]; the LH responses to GnRH of obese women increase with weight loss [38]; and LH levels, pulse amplitude; and response to GnRH are lower in obese than in nonobese PCOS [39]. The lower LH of obese PCOS women is partly attributable to increased LH clearance [40]. The available longitudinal data are compatible with excess adiposity after the onset of puberty slowing pubertal tempo in girls, though less so than prepubertal adiposity advances puberty onset [41–43]. Thus, these considerations raise the possibility that the excess adiposity of SPPOPA aggravates the relatively low LH production of slowly progressive precocity and contributes to the slow progression.

Since there is considerable evidence that excess adiposity advances the onset of puberty [2, 3, 44], it is possible that it paradoxically contributes to both the early onset of puberty in SPPOPA as well as to its slow progression thereafter. We speculate that overweight may be a factor in the precocity of girls in whom, like these, onset of puberty is only mildly premature; many sexually precocious girls in this 6–8 year age range do not require treatment to preserve height potential [1].

The limitations of this study should be kept in mind. It is descriptive and associative and should be considered exploratory. Furthermore, while the SPPOPA presentation is not rare, it is uncommon, and our group was small. Because our study was designed as a survey of the many aspects of puberty potentially disturbed in these young girls, our sleep data are sparse. In addition, we have not been able to obtain follow-up into the postmenarcheal stage of development in most. In spite of these limitations, our data indicate that mild peripubertal hyperandrogenism and excess adiposity do not predispose to elevated LH secretion during early puberty before menarche and are indeed compatible with the possibility of a suppressive effect of excess adiposity on circulating LH during puberty that deserves further study.

5. Conclusion

In summary, we demonstrate that sleep-related gonadotropin production and LH responses to GnRH agonist testing are blunted in girls with slowly progressive sexual precocity who are overweight and have premature adrenarche. These studies indicate that SPPOPA is a slowly progressive form of true puberty. In spite of maturational indices similar to OW-PUB, SPPOPA had lower LH responses to GnRHag. The data argue against the hypotheses that the prepubertal hyperandrogenism of excess adiposity or premature adrenarche enhance LH secretion or cause ovarian hyperandrogenism prior to menarche, although they seem to be modest risk factors for PCOS thereafter. These data are also compatible with the possibility that early pubertal girls are particularly sensitive to the gonadotropin-suppressive effects of excess fat mass, although obesity predisposes to the early onset of puberty.

Abbreviations

BMI: Body mass index
SPPOPA: Slowly progressive precocious breast development, overweight, and premature adrenarche
DHEA: Dehydroepiandrosterone
DHEAS: DHEA sulfate
GnRHag: GnRH agonist
HOMA: Homeostatic index model assessment of insulin resistance
OW-PUB: Overweight pubertal
PA: Premature adrenarche
PCOS: Polycystic ovary syndrome.

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