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ANOREXIA NERVOSA

Immaturity of the 24-Hour Luteinizing Hormone Secretory Pattern

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Abstract Nine women (17 to 23 years of age) with primary anorexia nervosa associated with amenorrhea had measurements of plasma luteinizing hormone concentrations at 20-minute intervals for 24 hours. Eight of the nine showed age-inappropriate secretory patterns that resembled those found in prepubertal and pubertal children. The finding of an "immature" luteinizing hormone pattern suggests that a "regression" (in the patients with secondary amenorrhea) or an "arrest" (in the patients with primary amenorrhea) of the luteinizing hormone secretory

"program" occurs in this disorder. One patient had a spontaneous remission, with return of body weight to normal, associated with a maturational change from the early pubertal luteinizing hormone pattern found during her illness to one characteristic of postmenarchal girls, indicating the reversibility of this abnormality. The finding of a relation between body weight and the maturity of the luteinizing hormone pattern supports the hypothesis that a "critical body weight" is an important factor in the initiation of menarche. (N Engl J Med 291: 861-865, 1974)

RECENT studies from this laboratory have delineated the sequential changes in the secretory patterns of plasma luteinizing hormone (LH) and follicle-stimulating hormone (FSH) during normal^{1,2} and abnormal^{2,3} sexual maturation. Prepubertal children show low levels of LH and FSH that oscillate around a constant mean. The onset of puberty in both boys and girls is heralded by the augmentation of LH secretion synchronous with sleep. This sleep-synchronized LH secretion in pubertal boys stimulates the Leydig cells to secrete testosterone during sleep.^{4,5} In adult men⁶ and post-menarchal women⁷ episodic LH secretion, of equal frequency and magnitude, occurs during waking and sleep periods. We studied the 24-hour LH secretory patterns in nine amenorrheic patients with primary anorexia nervosa as defined by Bruch⁸ to determine the maturational stage of their 24-hour plasma LH patterns.

Anorexia nervosa is primarily a disorder of young women characterized by marked weight loss, amenorrhea and hyperactivity in the presence of emaciation. The amenorrhea can precede, follow or appear coincidentally with the weight loss. Previous investigators have found low plasma^{9,10} and urinary gonadotropins¹¹ and an absent

response to clomiphene citrate during the acute phase of the disease.¹² Recently, two studies^{13,14} have documented the normal release of LH and FSH after administration of the gonadotropin releasing hormone. These data suggest that the site of the abnormality in gonadotropin regulation is the central nervous system. To gain additional insight into this disordered control of LH secretion, we measured plasma LH at 20-minute intervals for 24 hours in nine young women with primary anorexia nervosa.

MATERIALS AND METHODS

Patients

Our nine patients with anorexia nervosa, between 17 and 23 years of age, all had amenorrhea. Six had secondary, and three primary amenorrhea. They were all referred for evaluation of avoidance of food with severe weight loss. A complete medical evaluation showed no organic abnormality that could explain the marked weight loss and aberrant dieting and eating habits. The pertinent historical and clinical findings in the nine patients are summarized in Table 1. The degree of weight loss estimated as the percentage below their ideal weight for height and age (as determined from the standards of the Metropolitan Life Insurance Company of New York) ranged from 23.8 to 40.5 per cent.

Twenty-four Hour, 20-Minute Interval Sampling Studies

All nine patients with anorexia nervosa and representative normal prepubertal, early pubertal and late pubertal girls were admitted to the Clinical Research Center, Montefiore Hospital and Medical Center, for 20-minute interval plasma sampling studies for 24 hours and polygraphic recording of sleep according to protocols that have been published previously in detail from this laboratory.¹⁵ The sleep records were scored according to standardized criteria.¹⁶ One patient (Case 5) was studied on a second occasion six months after the first study, after return of body weight to normal and clinical remission.

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Table 1. Clinical Characteristics of Patients with Anorexia Nervosa.

CASE No.	AGE	HEIGHT	WEIGHT AT TIME OF STUDY	IDEAL WEIGHT	% DIFFERENCE FROM IDEAL	MENSTRUAL HISTORY	WEIGHT HISTORY
	yr	cm	kg	kg			
1	21	160	31.8	53.5	40.5	Menarche at age of 14, secondary amenorrhea 12 mo before study.	Weighed 54.5 kg until 14 mo before study & lost 20 kg over 1 yr.
2	19	166	35.0	56.9	38.6	Menarche at age of 12, with regular menstrual periods until 7 mo before study; similar episode of anorexia 3 yr before associated with amenorrhea.	Except for weight loss associated with previous episode of amenorrhea weighed 56.8 kg until 10 mo before admission (21.8-kg weight loss)
3	22	155	35.0	50.8	31.1	Primary amenorrhea until age of 16, when treatment with progesterone & estrogen begun, no spontaneous menstrual period.	Began to lose weight at age of 13, continuing until age 17, when she weighed 25 kg; during past 5 yr weight never > 37 kg.
4	19	162	40.0	54.4	26.5	Primary amenorrhea	Weighed 63.5 kg at age of 16, when she became vegetarian; stabilized at 47.5 kg until 6 mo before study, when she lost 7.5 kg.
5	22	158.5	40.2	52.8	23.8	Menarche at age of 14, with regular periods until age of 18 & then 6 mo of amenorrhea, which ended spontaneously; last menstrual period 2½ yr before study	Weight history obscure; weighed 50 kg at age of 14 but no memory of weight at time of onset of anorexia about 2½ yr before study.
	22½	158.5	50.7	52.8	4.0		
6	17	164	35.0	55.7	37.1	Menarche at age of 14; secondary amenorrhea from 15.3 yr of age.	14-kg weight loss over 18 mo period; weighed 39.0 kg 15 mo before study
7	23	172	42.6	60.8	33.5	Menarche at age of 13, with regular periods for 2 yr; menstrual periods then became irregular until they stopped 13 mo before study.	Began dieting at age of 15-16; maximum weight 63.5 kg, & minimum 42.5 kg.
8	17	159	33.7	51.9	35.1	Menarche at age of 12½ yr; periods always irregular & stopped 7 mo before study.	Lost 14.8 kg 12 mo before admission & study
9	20	152.5	37.2	49.0	24.1	Primary amenorrhea	Patient weighed approximately 45 kg at age of 13 but had weight loss since age of 14, never achieving more than 47 kg in weight

Plasma LH Measurements

Plasma LH was measured by the double-antibody radioimmunoassay described by Midgley¹⁷ as modified in our laboratory.⁶ Results are expressed in terms of the Second International Reference Preparation of Human Menopausal Gonadotropin (2d IRP-HMG). The LH radioimmunoassay (RIA) is capable of detecting 0.2 mIU as significantly different from zero, so that the minimum sensitivity in 200 µl of plasma is 1 mIU per milliliter. All plasma samples from each 24-hour study were assayed simultaneously, and the two studies in Case 5 were assayed simultaneously so that an accurate comparison between the two studies could be made. Student's *t*-test was used to assess statistical significance between the mean LH concentrations with subjects asleep and those with subjects awake.

RESULTS

Normal Subjects

Figure 1 shows characteristic LH secretory patterns in a normal prepubertal (lower panel) and early pubertal premenarchal girl (upper panel). Figure 2 shows the LH secretory pattern in a normal late pubertal premenarchal girl.

Anorexia Nervosa

Three 24-hour LH patterns were found, as follows:

Prepubertal patterns. Figure 3 shows the 24-hour LH secretory pattern in Case 1, a 21-year-old woman with anorexia nervosa. The similarity of the LH concentrations and secretory pattern to those of the normal prepubertal girl (Fig. 1, lower panel) is striking. The mean (\pm S.D.) LH concentration during sleep was 2.6 ± 0.5 as compared with 2.3 ± 1.0 mIU per milliliter during

waking (not significant).^{*} This patient was particularly noteworthy because she had been able to conceive normally three years before the onset of her illness and before noteworthy weight loss had occurred. Low prepubertal LH concentrations and the absence of episodic LH secretion during both sleep and waking periods was also found in Cases 2 and 3 (Table 2). Although there was no significant difference between the mean LH concentration asleep and that during waking in Case 4 (Table 2), the absolute levels were somewhat higher than those in Cases 2 and 3; nevertheless, they were lower than those found in normal adult menstruating women.¹⁸

Early pubertal patterns. Figure 4 shows the LH secretory pattern in Case 8, a 17-year-old girl with anorexia nervosa and secondary amenorrhea. The low waking LH concentrations increased two to three times after the onset of sleep. This type of LH secretory pattern is characteristic of normal early pubertal girls (upper panel, Fig. 1). This increased LH secretory activity during sleep resulted in a mean (\pm S.D.) LH concentration of 6.1 ± 1.8 mIU per milliliter as compared with 3.8 ± 0.9 mIU per milliliter during waking ($p < 0.001$). This characteristic early pubertal LH secretory pattern was also found in Cases 5, 6, 7, and 8 (Table 2).

Late pubertal pattern. Figure 5 shows the LH secretory pattern in Case 9, a 20-year-old woman with anorexia nervosa and primary amenorrhea. The augmented LH secretion during sleep resulted in a mean (\pm S.D.) LH concentration of 26.0 ± 10.1 as compared with 13.2 ± 3.7 mIU per milliliter during waking ($p < 0.001$). The marked augmentation of LH secretion during sleep as well

^{*}Although the absence of a significant difference between the mean LH concentration asleep and that waking is found in post-menarchal women, the absolute 24-hour mean (\pm SD) LH concentrations are significantly higher (10.2 ± 3.8).

as the presence of episodic LH secretion during waking is the characteristic 24-hour pattern of normal late pubertal premenarchal girls (Fig. 2).

Remission in patient with anorexia nervosa. The upper panel of Figure 6 shows the LH secretory pattern during the acute-illness phase of anorexia nervosa in a 22-year-old woman (Case 5). The mean (\pm S.D.) LH concentration during sleep was 3.5 ± 0.7 as compared with 3.0 ± 0.7 mIU per milliliter during waking ($p < 0.01$). A spontaneous remission occurred after graduation from college, associated with a 10.5-kg weight gain, bringing her body weight to 96 per cent of her ideal weight. She was restudied (lower panel, Fig. 6), and the normal adult pattern of episodic

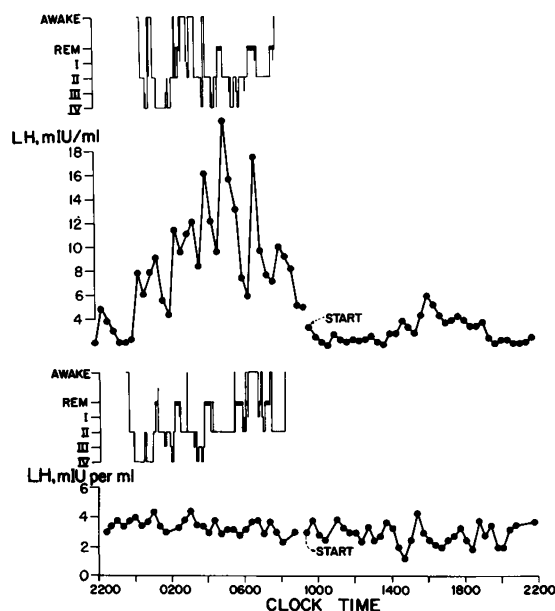


Figure 1. Plasma LH Concentration Every 20 Minutes for 24 Hours in a Normal Prepubertal Girl (Lower Panel) and Early Pubertal Girl (Upper Panel).

The sleep histogram is shown above the period of nocturnal sleep. Sleep stages are awake, rapid eye movement (REM) = —, stages I-IV by depth of line graph. Plasma LH concentrations are expressed as milli-international units per milliliter of Second International Reference Preparation of Human Menopausal Gonadotropin.

secretion of LH of equal magnitude during sleep — 8.2 ± 2.9 — and waking periods — 9.0 ± 2.5 — was found. At that time, a five-day course of clomiphene citrate (50 mg daily) was administered that initiated normal cyclic menses. The results of this study show that the abnormal LH secretory pattern found during an acute episode of anorexia nervosa associated with marked weight loss returns to normal when body weight is raised to normal.

DISCUSSION

This study was designed to evaluate the 24-hour LH secretory patterns in nine patients with primary anorexia nervosa. Eight of the nine studied showed patterns that resembled those of either normal prepubertal or pubertal, premenarchal girls. These LH secretory patterns inappropriate for the patient's chronologic age suggested that a "regression" (in the patients with secondary amenorrhea) or an "arrest" (in the patients with primary amenorrhea) of the normal LH secretory "program" oc-

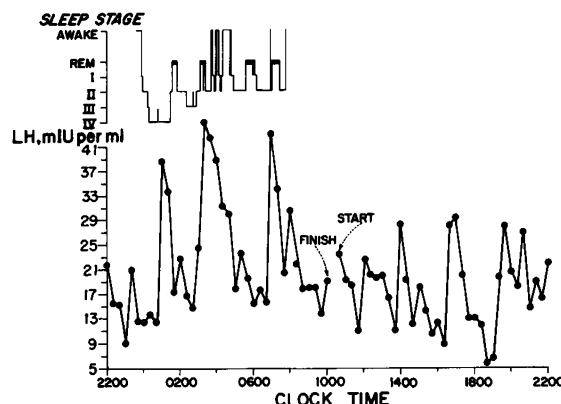


Figure 2. Plasma LH Concentration Measured Every 20 Minutes for 24 Hours in a Normal Late Pubertal Girl.

curs in this disorder. The "maturation" from an early pubertal LH secretory pattern to one characteristic of adult women in Case 5, after a return of body weight to normal and clinical remission, indicates the importance of body weight as one of the determinants of the functional integrity of the hypothalamic pituitary gonadal axis.

To prove definitively that the weight loss is the critical determinant responsible for the "immaturity" of the LH secretory pattern found in these patients, it will be necessary to study patients who show the behavioral aberrations of anorexia nervosa but before significant weight loss has occurred. Recent unpublished findings from our laboratory indicating that post-menopausal women with similar degrees of weight loss show premenopausal LH values as well as pubertal LH patterns support the hypothesis that the weight loss rather than the psychiatric abnormality is responsible for the LH findings in our patients with anorexia nervosa.

Although urinary and plasma gonadotropins have been shown to be uniformly low in patients with anorexia nervosa, it has not been clear whether the low value is due to abnormal pituitary or central-nervous-system function. Recently, two groups of investigators have shown that the gonadotropin releasing hormone (Gn-RH) causes the normal release of LH and FSH in most patients with anorexia nervosa.^{13,14} These data suggest that the gonadotropin abnormality is probably of central-nervous-

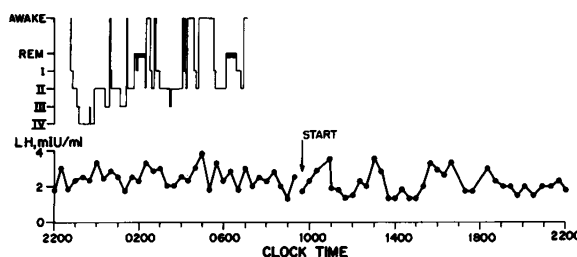


Figure 3. Plasma LH Concentration Every 20 Minutes for 24 Hours in Case 1 with Anorexia Nervosa and Secondary Amenorrhea.

Table 2. Plasma LH Concentrations (Mean \pm S.D.) during Sleep and Waking in Patients with Anorexia Nervosa.

CASE NO.	AGE yr	LH mIU/ml		COMMENT
		SLEEPING	AWAKE	
1	21	2.6 \pm 0.50	2.3 \pm 1.0	
2	19	4.2 \pm 0.53	4.6 \pm 0.53	
3	22	4.6 \pm 1.4	4.1 \pm 1.3	
4	19	6.9 \pm 1.1	6.6 \pm 0.82	
5	22	3.5 \pm 0.70*	3.0 \pm 0.70	
	22½	8.4 \pm 2.9	9.0 \pm 2.5	After weight gain & clinical remission
6	17	5.2 \pm 0.96†	4.7 \pm 0.80	
7	23	5.9 \pm 1.5†	5.2 \pm 1.1	
8	17	6.1 \pm 1.8‡	3.8 \pm 0.9	
9	20	26.0 \pm 10.1‡	13.2 \pm 3.7	

*Mean sleep LH concentration significantly higher ($p < 0.01$) than mean LH awake.

†Mean sleep LH concentration significantly higher ($p < 0.05$) than mean LH awake.

‡Mean sleep LH concentration significantly higher ($p < 0.001$) than mean LH awake.

system origin. Marshall and Fraser¹² reported that during the acute phase of anorexia nervosa, plasma LH levels were low and failed to rise after clomiphene citrate administration; however, after a return of body weight to normal clomiphene citrate responsiveness was restored, often in association with the return of cyclic menses. It has also been shown that the capacity to respond to clomiphene citrate is acquired during middle to late puberty.^{19,20} Since the 24-hour LH secretory pattern during the acute phase of anorexia nervosa most frequently resembles that of prepubertal or early pubertal, premenarchal girls, an absent response to clomiphene citrate would be expected. After body weight is raised to normal, with "maturation" of the LH secretory pattern to the adult type, a normal response to clomiphene citrate occurs.¹²

A "spin-off" of the results of the present study relates to the evidence that it provides that changes in body weight* may affect the spontaneous 24-hour LH secretory pattern, and have a relation to the sequential changes that oc-

*Although body weight is used body composition and in particular the relative degree of fatness is probably the critical determinant.²¹

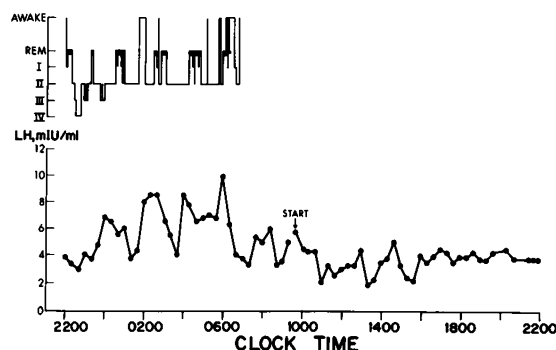


Figure 4. Plasma LH Concentration Every 20 Minutes for 24 Hours in Case 8 with Anorexia Nervosa and Secondary Amenorrhea.

cur in the LH secretory pattern during normal sexual maturation. Frisch and Revelle²² proposed that the onset of menarche is related to the attainment of a "critical" body weight. These authors showed that although the age of menarche had decreased from 16.5 to 12.5 years over the preceding 125 years, the mean weight at menarche remained unchanged at 47.8 ± 0.51 kg. They suggested that this "critical" weight is coupled with a change in the metabolic rate and associated with a decrease in the sensitivity of the hypothalamic-pituitary axis to circulating sex steroids. These changes then lead to an increase in gonadotropin secretion and the subsequent gonadal secretion of sex steroids.²³

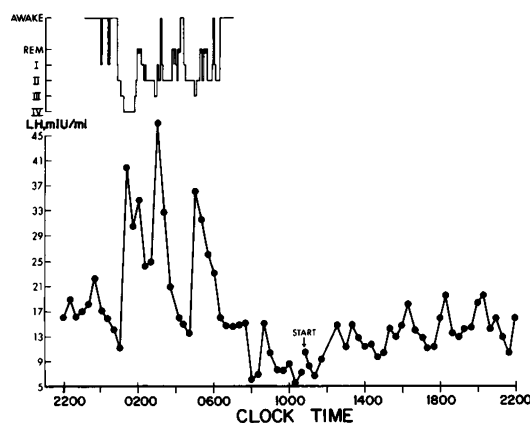


Figure 5. Plasma LH Concentration Every 20 Minutes for 24 Hours in Case 9 with Anorexia Nervosa and Primary Amenorrhea.

We recently reported that two boys (8 6/12 and 5 10/12 years of age) with untreated congenital adrenal hyperplasia and an advanced bone age had 24-hour LH secretory patterns that were indistinguishable from those of normal older pubertal children.² It was suggested that the prolonged exposure to excessive amounts of adrenal androgens resulted in an accelerated central-nervous-system maturation and a premature initiation of the normal pubertal 24-hour sleep-waking LH secretory pattern. Since these two boys also had body weights comparable to those of normal older pubertal boys this factor could have been the critical one responsible for the initiation of central-nervous-system puberty. One could postulate that any mechanism that leads to a critical increase or decrease in body weight would result in the corresponding initiation or "regression" of the pubertal LH secretory pattern.

Crisp has suggested that anorexia nervosa results from a phobia of the responsibilities and consequences of sexual maturation, with the consequent avoidance of the normal adolescent weight gain.²⁴ The disorder thus pivots around the maturational changes of puberty and their psychologic as well as sexual implications for the patient. The finding of a "regression" or "arrest" of at least one of the normal maturational events of puberty (i.e., the LH secretory pattern) provides a possible biologic mechanism for the avoidance of these conflicts. Return of body weight

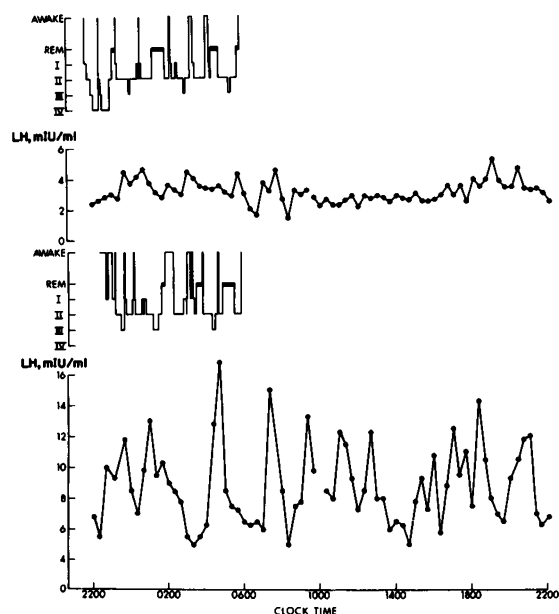


Figure 6. Plasma LH Concentration Every 20 Minutes for 24 Hours in Case 5 during Acute Exacerbation of Anorexia Nervosa (Upper Panel) and after Clinical Remission with Return of Body Weight to Normal (Lower Panel).

to normal and clinical remission are associated with maturation of the age-inappropriate LH secretory pattern to the "mature" adult pattern associated with normal cyclic menses and reproductive capacity.

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