

AMENORRHEA SECONDARY TO VOLUNTARY W

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ABSTRACT

Patients with voluntary weight loss not only may develop secondary amenorrhea like women with anorexia nervosa but apparently also have similar endocrine findings. Six young women who voluntarily dieted to lose from 13-50 pounds, including 4 from an obese weight, were evaluated because of no cervical mucus ferning, hypoestrogenic vaginal smears, and failure to have withdrawal menses from a progestogen. Serum FSH was normal in all while 4 had normal serum LH and 2 had low serum LH. T_4 and/or T_3 uptake was normal in all. The pituitary-adrenal axis was apparently intact since baseline urinary steroids were normal as was the response to both ACTH and metyrapone. Fasting serum growth hormone was markedly elevated in 2, slightly elevated in 3, with the other patient demonstrating an unusually high response to glucogan/propranolol in the 30 minute specimen. Voluntary weight loss amenorrhea is similar to anorexia nervosa except for the associated psychiatric abnormality.

The etiology of secondary amenorrhea may be multiple including hyperandrogenic states such as polycystic ovaries, ovarian or uterine failure, hypopituitarism, hypothalamic disorders, neurologic disease, or psychogenic causes. Cessation of menses following weight loss associated with anorexia nervosa has been known for many years and the amenorrhea may even precede the weight loss.¹⁻⁴ Not only can involuntary starvation induce secondary amenorrhea but also voluntary weight-reduction may result in cessation of the menstrual flow.⁵⁻⁷ Obese women that voluntarily lose to a desirable or even slightly subnormal weight may remain amenorrheic for a considerable time after weight reduction has stabilized. They may present with an endocrine pattern similar to patients with anorexia nervosa without the associated psychiatric abnormalities. All women with secondary amenorrhea need a minimal evaluation to include vaginal hormonal cytology and cervical mucus for presence of ferning. If these tests indicate hypoestrogenism and are confirmed by failure of withdrawal menses to a progestogen, further endocrine evaluation is indicated.

MATERIALS AND METHODS

During a 2 year interval, 6 nulliparous young women, ages 14-21 years, were evaluated for prolonged amenorrhea following a self-imposed weight loss. Prior to their voluntary weight reduction, all had regular menses for one or more years. Two of these patients (GOR, LJT) were motivated to lose weight so that they could qualify for enlistment in the Air Force. None of the 6 used any anorexic drugs to assist them in weight reduction. Complete physical examination was performed along with vaginal hormonal cytology and ferning of the cervical mucus. Medroxyprogesterone acetate 10 mg for 5-7 days was given during one or more courses as an attempt to induce a menstrual period. All 6 were hospitalized and serum collected daily for radioimmunoassay of FSH and LH. Urine was collected on 2 consecutive days for assay of 17-ketosteroids and 17-hydroxycorticosteroids as a baseline followed by ACTH 40 I. U. intravenously by infusion. After a day of rest the metyrapone test was performed by giving 750 mg orally every 4 hours for 6 doses. The 24-hour urine collection was continued during metyrapone administration and

the following day. A growth hormone provocative test was performed in 5 utilizing glucagon 1 mg intramuscularly after propranolol 100 mg orally. L-dopa 500 mg orally was given to one patient (MS) instead of the glucagon/propranolol test. Serum thyroxine (T₄) and triiodothyronine (T₃) uptake were performed in all. X-ray tomography of the sella turcica was performed in 3 patients (LJT, CLS, MS). Laparoscopy was accomplished in one patient (MAS) during the initial evaluation and in another (GOR) 8 months after the initial evaluation.

RESULTS AND FINDINGS

All 6 women were amenorrheic from 4-36 months prior to the evaluation, had hypoestrogenic vaginal smears, absence of ferning in the cervical mucus, and failed to have withdrawal menses when given one or more courses of a progestogen (Table 1). The amenorrhea followed a voluntary weight loss of 13-50 pounds from a self-imposed weight reduction (Table 2). Weight loss not only ceased but had also remained stable for 3-24 months prior to evaluation, yet menses had not resumed. There were 4 patients who were initially obese and lost to a near normal

weight. The other two (MAS, CLC) voluntarily lost weight because of a desire for a thin body image. Their final weight was 79% and 86% of normal according to weight standards for females in AFR 160-43. This is the Air Force Regulation listing standard, minimum, and maximum weights for all military personnel.

Serum FSH was within the normal range for all 6 while 2 (MAS, MS) were found to have low serum LH (Table 3). All 6 were considered to be euthyroid since either the T₄ or T₃ uptake was normal. T₄ was slightly elevated in one (CLC) but the T₃ uptake was normal. T₃ uptake was slightly elevated in 2 (GOR, MS); however, the T₄ was within the normal range. Urinary 17-hydroxycorticosteroids were normal in all, increased with ACTH administration, and responded with at least a 3-fold rise during and following the metyrapone. Urinary 17-ketosteroids were normal in 4, slightly elevated in 2 (CLC, LLT), and increased as expected with metyrapone.

Fasting serum growth hormone was markedly elevated in 2 patients (GOR, LJT) and slightly elevated in 3 others (Table 4). Unfortunately, a laboratory accident precluded radioimmunoassay

of the fasting in one subject (LLT); however, the 30 minute specimen was markedly elevated to 39.2 ng/ml. All women undergoing the glucagon/propranolol provocative test for growth hormone had an increase in serum values although one subject (CLC) had a blunted response. The subject (MS) that had the L-dopa provocative test for growth hormone was considered to have an inadequate response although the fasting level was slightly elevated.

Ovarian biopsy performed during laparoscopy of one patient (MAS) at the time of initial evaluation was reported as "numerous primordial follicles." X-rays of the sella turcica were normal in all 3 of those studied (LJT, CLC, MS).

Treatment and Results: The patient (LLT) with the longest duration of amenorrhea and stabilized weight had a spontaneous resumption of menses before treatment was instituted. The other five women were treated with cyclic estrogen and progestogen. Ethinyl estradiol 0.02 mg was administered from the 1st-25th/month and medroxyprogesterone acetate 10 mg was given from the 19th-25th/month. Four patients are still receiving this therapy although one has discontinued

the medication because of evidence that normal function was restored. This patient (GOR) had laparoscopy 8 months after initial evaluation with findings of a corpus luteum, confirmed by ovarian biopsy.

DISCUSSION

Since amenorrhea is an important symptom of anorexia nervosa, secondary amenorrhea in the setting of weight loss must be carefully evaluated. Our 6 patients did not have anorexia nervosa since all voluntarily dieted and lost weight, 4 from an obese weight to that which was nearly normal. None were emaciated although 2 were underweight. All 6 desired some thinness of body image and 2 were motivated to lose weight so that they could enlist in the Air Force. Detailed psychiatric investigations were not performed on our patients but intensive evaluations have been reported by others.⁴

A normal pituitary-adrenal axis was demonstrated in our 6 patients by normal baseline urinary 17-hydroxycorticosteroid and 17-ketosteroids with the expected response to metyrapone. Patients with anorexia nervosa have also been found to have

normal responses to metopirone and ACTH.^{2, 5, 9} Thyroid function with normal serum T₄ and T₃ uptake was found in our patients which has also been reported in patients with anorexia nervosa.^{1, 2, 3}

Serum LH and FSH values in our 6 women were normal to low indicating normal but acyclic pituitary function without gonadal failure. Patients with anorexia nervosa and weight loss amenorrhea have been reported to have low to normal LH and FSH levels.^{2, 3, 5, 6, 7, 9, 10, 11} No attempt to measure pituitary responsiveness to LH-RH was made in our study, but has been reported to be delayed in both patients with anorexia nervosa and simple weight loss.⁷

All 6 of our patients had a growth hormone stimulation test either to glucagon or L-dopa. Surprisingly, the 5 women tested had elevated fasting growth hormone levels. The fasting serum growth hormone level is usually undetectable (< 0.4 ng/ml) in our laboratory for normal women. Patients with anorexia nervosa have elevated fasting growth hormone levels in the range of our patients.^{3, 10, 12} The finding of elevated fasting serum

growth hormone levels has not been documented previously in patients with voluntary weight loss amenorrhea.

Gonadal function in our patients was evaluated by vaginal cytology, examination of the cervical mucus, and administration of an oral progestogen. All six women had hypoestrogenic vaginal smears which is in agreement with the work of others (1, 2, 5, 6, 9). Cervical mucus was very scant with no evidence of ferning. None of the 6 had withdrawal bleeding to the progestogen. These 3 tests demonstrate lack of sufficient estrogen production by the ovaries.

Treatment consisted of ethinyl estradiol 0.02 mg from the 1st-25th of each month with a progestin added from the 25th of the month. This resulted in regular withdrawal menses. This dosage of estrogen was chosen because not only does it suppress the hypothalamic-pituitary axis but also may exert positive feedback to the pituitary. Some confirmation of the suppressive effect was obtained by the finding of a corpus luteum in one patient still receiving this low-dosage estrogen therapy. This patient had not gained weight since the initial evaluation.

Another of our patients (LLT) resumed spontaneous menses after 3 years of amenorrhea and 2 years at a stabilized lower weight. Further work must be done to determine the complete clinical course in patients with voluntary weight loss amenorrhea. However, it appears that in time return of normal ovarian function may be established at the new, lower weight. This supports the work of other authors.⁵

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Table 1. CLINICAL CHARACTERISTICS

Patient	Age	Duration of Amenorrhea	Vaginal Smear	Cervical Mucus	Response to Progestogen
MAS	14	11 Months	Hypoestrogenic	No Fern	No Menses
GOR	18	4 Months	Hypoestrogenic	No Fern	No Menses
LJT	18	4 Months	Hypoestrogenic	No Fern	No Menses
CLC	19	8 Months	Hypoestrogenic	No Fern	No Menses
LLT	20	36 Months	Hypoestrogenic	No Fern	No Menses
MS	21	13 Months	Hypoestrogenic	No Fern	No Menses

Table 2. WEIGHT LOSS

Patient	Initial Weight	Loss	Final Weight	Stabilized		Height	Normal Weight*	% Norm
				Weight	Weight			
MAS	107 lbs	14 lbs	93 lbs	11 Months	11 Months	66"	118 lbs	79%
GOR	170 lbs	50 lbs	120 lbs	4 Months	4 Months	62"	107 lbs	112%
LJT	185 lbs	49 lbs	136 lbs	3 Months	3 Months	68"	125 lbs	109%
CLC	118 lbs	13 lbs	105 lbs	6 Months	6 Months	67"	122 lbs	86%
LLT	190 lbs	50 lbs	140 lbs	24 Months	24 Months	64"	111 lbs	126%
MS	165 lbs	40 lbs	125 lbs	13 Months	13 Months	67"	112 lbs	102%

*AFR 160-43 (see Text)

Table 2. WEIGHT LOSS

Patient	Initial Weight	Loss	Final Weight	Stabilized Weight	Height	Normal Weight*	% Normal
AS	107 lbs	14 lbs	93 lbs	11 Months	66"	118 lbs	79%
DR	170 lbs	50 lbs	120 lbs	4 Months	62"	107 lbs	112%
JT	185 lbs	49 lbs	136 lbs	3 Months	68"	125 lbs	109%
LC	118 lbs	13 lbs	105 lbs	6 Months	67"	122 lbs	86%
LT	190 lbs	50 lbs	140 lbs	24 Months	64"	111 lbs	126%
MS	165 lbs	40 lbs	125 lbs	13 Months	67"	112 lbs	102%

*AFR 160-43 (see Text)

Table 3. LABORATORY DATA

Patient	Serum FSH* (mIU/ml)	Serum LH* (mIU/ml)	T4 (µg/100 ml)	T3 Uptake	17-Hydroxycorticosteroids** (mg/24 hrs)		17-Ketosteroids** (mg/24 hrs)	
					Baseline	Metopirone	Baseline	Metopirone
MAS	9.2	2.3	7.0	31.2%	4.5	17.5	3.5	10.5
GOR	8.4	9.8	6.7	37.8%	6.5	25.5	7.5	12.0
LJT	3.9	4.6	4.6	28.9%	14.1	41.7	9.1	21.5
CLC	6.7	12.5	12.7	34.3%	8.5	31.0	15.0	16.5
LLT	9.9	7.5	8.7	32.7%	8.5	34.0	20.6	33.5
MS	7.7	1.1	8.3	42.3%	4.0	20.0	11.0	14.5
al Values 4-10		5-12	4-11	25-35%	4-12	-	4-12	-

*Mean of 5-9 specimens

**Mean of 2 specimens

Table 4. SERUM GROWTH HORMONE (ng/ml) RESPONSE TO GLUCAGON/PROPRANOLOL

Patient	Fasting	30 min	1 hr	90 min	2 hrs	3 hrs
MAS	5.3	>20	>20	>20	>20	>20
GOR	16.5	3.6	2.6	1.3	6.5	7.5
LJT	29.0	26.7	26.5	28.0	23.0	6.3
CLC	3.8	1.3	1.2	3.0	6.5	2.2
LLT	-	39.2	-	7.5	10.0	4.7
MS*	3.7	2.1	1.3	0.3	0.4	0.4
Normal Values	0-3	Increase to 7-20 within 3 hours				

*L-dopa 500 mg orally