Aetiology, previous menstrual function and patterns of neuro-endocrine disturbance as prognostic indicators in hypothalamic amenorrhoea

Rebecca B. Perkins, Janet E. Hall and Kathryn A. Martin

Reproductive Endocrine Unit and National Center for Infertility Research, Massachusetts General Hospital, 55 Fruit Street BHX 5, Boston, MA 02114, USA

BACKGROUND: Hypothalamic amenorrhoea (HA) is a syndrome associated with infertility and osteopenia in reproductive-age women. METHODS: To understand better the natural history of this disorder, 28 women participated in a retrospective, questionnaire-based analysis to elucidate factors associated with spontaneous recovery. RESULTS: 54% of subjects developed HA related to an eating disorder, 21% related to stress/weight loss, and 25% without obvious contributing factors (idiopathic). HA associated with a clear precipitant had a better prognosis than idiopathic HA (71 versus 29% recovery; \( P < 0.05 \)). Reversal of the inciting factor appeared necessary but not sufficient for recovery (83% recovery if factor reversed). Normal menarche occurred in 61% of subjects, oligomenorrhoea in 32%, and primary amenorrhoea in 7%. Oligomenorrhoea and normal menarche showed a trend toward better prognosis than primary amenorrhoea (NS). Compared with controls, 46% of HA patients had decreased frequency of LH pulses, 7% decreased amplitude, 18% decreases in both frequency and amplitude, 18% absent pulses, and 11% normal-appearing pulses. Pulse pattern at baseline did not predict recovery. CONCLUSIONS: The aetiology of HA at the time of presentation predicts subsequent recovery of menstrual function. In stress, weight loss, or eating disorder-related HA, rates of recovery exceeded 80% when precipitating factors were reversed. Idiopathic HA may represent a different disorder as recovery rates were <30%.

Key words: aetiology/hypothalamic amenorrhoea/neuro-endocrine/recovery

Introduction

The clinical syndrome of hypothalamic amenorrhoea (HA) is characterized by amenorrhoea, hypo-oestrogenism, low or normal serum gonadotrophins, and a broad spectrum of abnormal patterns of hypothalamic gonadotrophin-releasing hormone (GnRH) secretion (Reame et al., 1985; Santoro et al., 1986; Perkins et al., 1999). HA accounts for 34% of secondary amenorrhoea (Reindollar et al., 1986), and is of clinical importance because the anovulation associated with HA precludes the possibility of achieving pregnancy without therapy (Martin et al., 1990) and the hypo-oestrogenic state associated with HA often results in osteopenia (Biller et al., 1991; Fabbri et al., 1991). HA has been associated with increased levels of exercise in female athletes (Feicht et al., 1978; Samuels et al., 1991; DeCree, 1998) regardless of percentage of body fat (Russell et al., 1984; Constantini and Warren, 1995). In non-exercising women, HA has been associated with weight loss (Nakamura et al., 1985; Kotsuji et al., 1993), even when women never dropped below the normal range of weight for height (Graham et al., 1979; Levine et al., 1994). Psychological stress has been cited as a causal factor in some cases (Hirvonen, 1977; Reindollar et al., 1986), and recent studies provide evidence for higher levels of dysfunctional attitudes, difficulty coping with stress (Giles and Berga, 1993), lower self-esteem, and a higher prevalence of psychological disturbances (Brown et al., 1983) in women with HA when compared with eumenorrhoeic controls and controls with amenorrhoea due to other causes. The association of amenorrhoea with anorexia nervosa is well established, and menstrual disturbances often begin prior to significant weight loss (Warren and van de Wiele, 1973; Fries, 1977; Falk and Halmi, 1982) and persist after recovery to normal weight (Golden et al., 1997; van Binsbergen et al., 1990; Garcia-Rubi et al., 1992).

The ability of most women to retain normal menstrual cycles in the setting of stress, weight loss, or exercise suggests that women who develop HA have an underlying susceptibility to amenorrhoea. Previous studies indicate that menstrual patterns after menarche (referred to subsequently as primary menstrual function) might be linked to the development of HA later in life. One study of 262 patients with secondary amenorrhoea found menstrual irregularities prior to the onset of amenorrhoea in 10–20% of patients who developed HA, but found no evidence of prior menstrual irregularities in...
women with amenorrhoea related to Cushing’s syndrome, hypothyroidism, Sheehan’s syndrome, pituitary tumours, or Asherman’s syndrome (Reindollar et al., 1986). Other work indicates that athletes with prior menstrual irregularities are more susceptible to developing amenorrhoea than those with normal cycles at baseline (DeCree, 1998).

Regardless of aetiology, HA is associated with a number of neuro-endocrine abnormalities involving the hypothalamic GnRH pulse generator. Some studies report a lower mean frequency of LH pulses in HA patients than in normally cycling women (Khoury et al., 1987; Berga et al., 1989), while previous work, including our own, has demonstrated a broader neuro-endocrine spectrum ranging from complete absence of LH pulsations to normal-appearing secretion patterns (Reame et al., 1985; Santoro et al., 1986; Perkins et al., 1999). Furthermore, LH secretion patterns often vary within an individual over time (Reame et al., 1985; Santoro et al., 1986; Perkins et al., 1999) in the absence of clinical change or menstrual resumption.

Because the duration of amenorrhoea influences the likelihood that a patient will develop osteopenia (Biller et al., 1991), the probability of recovering menses spontaneously is central to issues of treatment. Large longitudinal follow-up studies of 90–240 patients with HA related to weight loss have shown recovery rates ranging from 33% after 3 years (Nakamura et al., 1985) to 72% after 6 years (Hirvonen, 1977). Recovery of spontaneous menses following anorexia nervosa range from 56% after 6 years in an adult population (Hirvonen, 1977), to 68% after 1 year in an adolescent population (Golden et al., 1997). The only published follow-up of psychogenic and idiopathic HA cites 6 year recovery rates of 72 and 61% respectively (Hirvonen, 1977). Relationship of menstrual recovery to weight recovery in previous studies has been unclear due to relatively short follow-up and possible confounding psychological factors (Brown et al., 1983; Nakamura et al., 1985; Kotsuji et al., 1993). No study has yet explored the question of whether primary menstrual function or GnRH pulse patterns during amenorrhoea may predict subsequent recovery from HA.

The design of the current study allowed intensive examination of factors affecting HA development and recovery in 28 patients, and addressed the following hypotheses: (i) women who develop HA in response to inciting factors have higher rates of recovery than women who develop HA in the absence of identifiable triggers, and this recovery is associated with reversal of the inciting factor, (ii) women with regular menstrual cycles prior to developing HA have a higher recovery rate than those who never established regular menstrual cycles, and (iii) women with normal-appearing LH secretion patterns have a higher recovery rate than women with highly abnormal patterns of LH secretion.

Materials and methods

Baseline

Subjects
All subjects participated in frequent-sampling neuro-endocrine studies in our unit between 1979 and 1997. All baseline and follow-up studies were approved by the Institutional Review Board of Massachusetts General Hospital and informed consent was obtained from each subject prior to each study. HA was defined, as previously described (Crowley et al., 1985; Santoro et al., 1986; Perkins et al., 1999), as a history of secondary amenorrhoea of at least 6 months duration with low or normal gonadotrophins, or a history of primary amenorrhoea with low or normal gonadotrophins and normal central nervous system (CNS) imaging. Women with complete congenital GnRH deficiency either with anosmia (Kallmann’s syndrome) or without anosmia (idiopathic hypogonadotrophic hypogonadism) were excluded from this study. At the time of the neuro-endocrine study, subjects had no systemic illness, galactorrhoea, hirsutism, or ovarian enlargement, and had a normal baseline complete blood count, ferritin, thyroid function tests, prolactin, and free testosterone. All subjects weighed between the 10th and 90th percentile for height (Sargent, 1963), reported no current eating disorder, and had no admitted history of excessive exercise (defined as at least 20 miles/week of running or equivalent) (Feicht et al., 1978). However, detailed assessment of eating disorder pathology was not obtained at that time. Women with clinical stigmata or LH pulse patterns consistent with polycystic ovarian syndrome (PCOS) were excluded from the study. Subjects were not screened by ultrasound for ovarian PCO morphology.

Baseline sampling study
Pulsatile LH secretion was assessed from frequent sampling studies in which blood was sampled every 10 min for 8–24 h. Two studies, which occurred prior to 1982, used a 20 min blood-sampling interval but were identical in all other respects. Plasma LH, FSH, oestradiol and progesterone concentrations were measured by radioimmunoassay, as previously described (Crowley et al., 1980; Filicori et al., 1984), and assay methodologies remained stable over the 20 year duration of the study. All samples from an individual study were measured in the same assay. The intra-assay coefficient of variation (CV) was estimated for each study by replicate measurements of a plasma pool from that study patient.

Data analysis
Pulses were determined using a previously validated modification of the Santen and Bardin method (Santen and Bardin, 1973; Hayes et al., 1999). The amplitude was calculated as the difference between the peak and the preceding nadir for each pulse. Undetectable values were assigned the lowest measurable assay values. A pulse was defined as a peak consisting of at least two points, in which the highest point met the criteria of 2 IU/l and three times the intra-assay coefficient of variation (%CV) above the nadir point, and a second point met at least one of those criteria. The frequency was expressed per 24 h. Values obtained for study subjects were compared with values for the early follicular phase (EFP) in 15 normally cycling women described previously (Filicori et al., 1986; Hall et al., 1992). Primary data for control subjects were obtained and re-analysed according to the criteria used in this study. Values from the EFP of a normal cycle were used for comparison because the low oestrogen and progesterone concentrations seen in HA most closely match the hormonal conditions present in the EFP of a normal menstrual cycle.

Longitudinal follow-up

Subject contact and data collection
From a pool of 45 women who completed baseline studies, 28 women participated in follow-up studies, 13 women could not be located, three women declined participation, and one died of an unrelated cause prior to follow-up. Participating subjects were contacted via letter and agreed to answer a three-part phone interview (n = 27) and/or questionnaire (n = 21) which addressed the topics of menstrual

Predictors of recovery in HA
The natural history of hypothalamic amenorrhoea: telephone interview and questionnaire summary

<table>
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<th>Table I. Summary of topics addressed in the phone interview and questionnaire</th>
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<td>The natural history of hypothalamic amenorrhoea: telephone interview and questionnaire summary</td>
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<tr>
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<tr>
<td>Age of menarche; subsequent menstrual pattern</td>
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<tr>
<td>Onset and perceived cause of amenorrhoea</td>
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<tr>
<td>Onset and perceived cause of menstrual resumption; subsequent menstrual pattern</td>
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<tr>
<td>2. Diet and exercise habits</td>
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<td>Current age, height, and weight</td>
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<td>Weight history</td>
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<tr>
<td>Exercise history</td>
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<td>Eating disorder history</td>
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<tr>
<td>3. Pregnancy history</td>
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<tr>
<td>Number of pregnancies, children, miscarriages</td>
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<tr>
<td>Methods used to achieve pregnancy</td>
</tr>
</tbody>
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history, current menstrual function, pregnancy history, diet and exercise history, and eating disorder history (Table I). Examples of questions asked include: ‘Do you attribute any cause to losing your periods?’ and ‘Have you ever been diagnosed with, or felt that you had an eating disorder, either anorexia, bulimia, or binge eating disorder?’ Further data was gathered from subjects’ hospital medical records, after informed consent was obtained.

Clinical definitions

Causal aetiology

The categories of stress/weight loss, eating disorder, and idiopathic were created based on the frequency with which these factors were self-reported as the events precipitating HA in subjects’ written and verbal self-reports and medical records. Although exercise is frequently seen as a cause of HA, it did not play a major role in this population as all heavily exercising subjects were excluded from the baseline study. Stress/weight loss was defined as a self-reported weight loss of at least 6.8 kg and/or an experience the subject reported as emotionally distressing which coincided with the onset and duration of amenorrhoea. Stress and weight loss were combined into one category due to the co-existence of both factors in the majority of patients. The eating disorder classification included subjects with clinical and subclinical eating disorder syndromes. A clinical syndrome of either anorexia or bulimia nervosa was defined as at least one of the following: (i) a written history of either anorexia or bulimia nervosa in the medical record, (ii) a self-reported eating disorder for which professional treatment was sought, and/or (iii) a minimum adult body mass index (BMI) of <17.5, defined as the anorectic weight range (World Health Organization, 1993) accompanied by symptoms of excessive dieting and weight preoccupation. Subclinical syndromes were defined, consistent with the DSM-IV criteria for eating disorder not otherwise specified (American Psychiatric Association, 1994), as symptoms of excessive dieting and weight loss, weight preoccupation, and amenorrhoea during which subjects did not reach a dangerously low weight and did not seek treatment related to their conditions. Idiopathic aetiology included subjects whose amenorrhoea could not reasonably be attributed to any medical, physical, or psychological factors.

Primary menstrual function

Each subject was also assigned to a category of primary menstrual function, either primary amenorrhoea, oligomenorrhoea, or normal menarche. Primary amenorrhoea was defined as a complete absence of spontaneous menses. Oligomenorrhoea was defined as the achievement of menarche between ages 10 and 18, followed by an irregular cycle pattern with an average cycle duration of >35 days (Speroff et al., 1994). Normal menarche was defined as the achievement of menarche between ages 10 and 18, followed by a regular cycle pattern with cycles averaging between 21 and 35 days in length prior to the development of HA (Speroff et al., 1994).

Neuro-endocrine pattern

Each subject received a neuro-endocrine classification based on the pattern of pulsatile LH secretion during her baseline study. LH secretion patterns were analysed and classified into the following categories as previously described (Perkins et al., 1999): (i) apulsatile, defined as the absence of LH pulsations, (ii) low amplitude, defined as a normal LH pulse frequency but a mean amplitude greater than one standard deviation below the mean amplitude in normal EFP controls (15.85% of a normal population will fall within this group), (iii) low frequency, defined as a normal mean LH pulse amplitude but an LH pulse frequency greater than one standard deviation below the mean frequency in normal EFP controls, (iv) low frequency/low amplitude, defined as both frequency and amplitude of LH pulses more than one standard deviation below the means in normal EFP controls, and (v) unclassified, defined as both frequency and amplitude of LH pulses within the normal range for women in the EFP.

Recovery

Recovery of normal menstrual function was defined as the occurrence of regular cycles with cycles averaging between 21 and 35 days (Speroff et al., 1994). Women who achieved oligomenorrhoea (average intermenstrual interval >35 days) following a period of complete amenorrhoea were not considered recovered.

Data analysis

Each parameter (causal aetiology, primary menstrual function, and neuro-endocrine pattern) was analysed with respect to the resumption of normal menstrual function. Fisher’s exact test was used to determine the significance of intergroup differences in recovery rates and (homoscedastic) t-tests were used to determine the significance of intergroup differences in physical/hormonal parameters. Values are expressed as the mean ± SEM unless specified, and the two-sided 0.05 level is considered significant unless otherwise noted.

Results

Baseline study

Baseline data provided below include those 28 subjects who participated in both a baseline frequent sampling study and a follow-up interview. Subjects who participated in both baseline and follow-up did not differ from those who did not participate in follow-up, in age, BMI, duration of amenorrhoea, or age at which HA developed. The mean age for the development of secondary HA in this group was 24.9 ± 1.2 years, (range = 15–34). At the time of neuro-endocrine study, subjects had a mean age of 29.4 ± 1.0 years (range = 21–38), had a mean BMI of 21.6 ± 0.7 kg/m² (range = 17.5–31.7), and had been amenorrhoeic for a mean of 5.1 ± 0.8 years (range = 0.5–15).

Aetiology

Six of the 28 women (21%) met the criteria for stress/weight loss (Figure 1). Four developed HA coincident with both stress and weight loss, one subject developed HA coincident with stress alone, and one subject developed HA coincident with weight loss alone. The mean weight loss achieved was 12.7 ± 4.1 kg, and the mean minimum BMI was 19.1 ± 0.4 kg/m². Stress was related to parental death in two cases,
Predictors of recovery in HA

Figure 1. Aetiology of HA: stress/weight loss (21%), eating disorder (54%), and idiopathic (25%). Note that subjects with a history of excess exercise were excluded from the initial study.

Figure 2. Primary menstrual function in HA: primary amenorrhoea (7%), oligomenorrhoea (32%), and normal menarche (61%).

work or school difficulties in two cases, and family difficulties in one case.

Fifteen of the 26 women (54%) developed HA coincident with a clinical or subclinical eating disorder. Average weight loss was 9.1 ± 1.3 kg, and did not differ significantly between women with clinical or subclinical syndromes. All women were within 10–90% of normal weight for height according to the Sargent scale and exercising <20 miles/week of running or equivalent at the time of baseline study.

Seven subjects (25%) could identify no factor that contributed to the development of amenorrhoea, and were assigned to the idiopathic category.

Primary menstrual function
Two subjects (7%) had primary amenorrhoea, and 26 subjects had secondary amenorrhoea, which was further subdivided into the categories of oligomenorrhoea (n = 9; 32%), and normal menarche (n = 17; 61%) (Figure 2). The mean age of menarche, excluding subjects with primary amenorrhoea, was 13.7 ± 0.6 years, with a range of 11–17 years.

Baseline neuro-endocrine pattern
At baseline, five subjects (18%) had apulsatile, two (7%) had low amplitude, five (18%) had low frequency/low amplitude, 13 (46%) had low frequency, and three (11%) had unclassified LH pulse patterns (Figure 3).

Longitudinal follow-up: predictors of recovery
At follow-up, subjects ranged in age from 28–52 years (mean 38.9 ± 1.3), and BMI ranged from 15.4–49.9 kg/m² (mean 23.5 ± 1.3). Average length of follow-up was 10.1 ± 0.9 years (range = 2–19), and was similar for all subgroups when aetiology, primary menstrual function, or neuro-endocrine pattern was considered. Eighteen of the 28 subjects had resumed normal cycling, four achieved at least one episode of spontaneous menstrual bleeding but never achieved regular cycles, and six remained completely amenorrhoeic. For those women who recovered normal menstrual function, age at resumption ranged from 24–43 years (mean 31.8 ± 1.3), and the duration of HA was 2.5–17 years (mean 7.5 ± 1.2).

Aetiology
All subjects whose onset of HA correlated with stress/weight loss resumed normal cycling (100% recovery). The stress and/or weight loss that precipitated HA resolved prior to menstrual resumption in all cases.

Four recoveries were associated with successful pregnancies. Two recoveries, which occurred in normal or overweight subjects, occurred in the absence of weight gain. Two recoveries, which occurred in underweight subjects, occurred coincident with post-partum weight gains of 4.5 and 13.2 kg respectively.

Nine of the 15 women (60%) who suffered from an eating disorder recovered normal menstrual function, three had some recovery of the hypothalamic–pituitary–ovarian axis but did not recover normal cycling patterns, one recovered normal cycles but relapsed into HA, and two remained completely amenorrhoeic. There was no difference in recovery rates between women with subclinical versus clinical eating disorder.
syndromes. In those women who recovered normal menstrual function, six recoveries were associated with weight gain alone (mean weight gain 10.2 ± 1.2 kg), and three recoveries were associated with a pregnancy during which patients regained weight and maintained this weight 6 months after pregnancy (mean weight gain 3.5 ± 0.4 kg). Of the three subjects who had some menstrual bleeding but did not achieve regular cycles, two are weight and symptomatically recovered, and one is currently underweight (BMI = 17.0 kg/m²). The subject, who recovered then relapsed, maintained regular cycles for 2.5 years while undergoing fluoxetine treatment for depression but ceased cycling after treatment was discontinued. Of the two amenorrhoeic subjects, one is still symptomatic and underweight (BMI = 15.4 kg/m²), and the other is mildly symptomatic and weight-recovered within the past year. Non-recovered subjects were not significantly thinner at the time of follow-up than recovered subjects (mean BMI of non-recovered = 20.0 ± 1.3 kg/m²; mean BMI of recovered = 22.0 ± 0.6 kg/m²).

Only two of the seven subjects (29%) with idiopathic HA recovered menstrual function (Table II). One subject recovered following several months of continuous treatment with pulsatile GnRH, and the other recovery occurred without obvious contributing factors.

Aetiology was a significant predictor of recovery, with idiopathic HA conferring a poor prognosis (Figure 4a). Recovery in the stress/weight loss group appeared to depend on reversal of the causal factor, either stress or weight loss. Weight gain and resolution of eating disorder symptoms appeared to be necessary for menstrual recovery in the eating disorder group, but were not sufficient for recovery in all cases.

**Primary menstrual function**

Two subjects presented with primary amenorrhoea. One subject, who presented without contributing factors and with a low amplitude pattern of LH secretion, never had a spontaneous menstrual period. The other subject, who presented with a low frequency pattern and developed an eating disorder 1 year following the diagnosis of primary amenorrhoea, developed an irregular pattern of cycling several years following weight and psychological recovery. Five of nine (56%) subjects with oligomenorrhoea resumed normal cycling, and 13 of 17 subjects (76%) with normal menarche resumed normal cycling (Figure 4b). Although the sample size was small, subjects with primary amenorrhoea showed a trend toward lower recovery rates than subjects who reported at least one episode of spontaneous menstrual bleeding (P = 0.09). Recovery rates in subjects with oligomenorrhoea did not differ significantly from those in subjects with normal menarche.

**Baseline neuro-endocrine pattern**

At follow-up, three of three (100%) subjects with unclassified patterns, nine of 13 (69%) subjects with low frequency patterns, three of five (60%) subjects with a apulsatile patterns, three of five (60%) subjects with low amplitude/low frequency patterns, and none of two (0%) subjects with low amplitude patterns recovered spontaneous menstrual function. No neuroendocrine pattern conferred prognostic significance. Mean LH

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### Table II. Individual characteristics of patients with idiopathic aetiologies

<table>
<thead>
<tr>
<th>Number</th>
<th>Neuroendocrine pattern</th>
<th>Primary menstrual function</th>
<th>Recovery of menstrual function</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Low amplitude</td>
<td>Primary amenorrhoea</td>
<td>No recovery</td>
</tr>
<tr>
<td>2</td>
<td>Low amplitude</td>
<td>Oligomenorrhoea</td>
<td>No recovery</td>
</tr>
<tr>
<td>3</td>
<td>Low amplitude/low frequency</td>
<td>Normal menarche</td>
<td>Normal cycles</td>
</tr>
<tr>
<td>4</td>
<td>Low frequency</td>
<td>Normal menarche</td>
<td>Normal cycles</td>
</tr>
<tr>
<td>5</td>
<td>Low frequency</td>
<td>Normal menarche</td>
<td>No recovery</td>
</tr>
<tr>
<td>6</td>
<td>Apulsatile</td>
<td>Normal menarche</td>
<td>No recovery</td>
</tr>
<tr>
<td>7</td>
<td>Apulsatile</td>
<td>Oligomenorrhoea</td>
<td>No recovery</td>
</tr>
</tbody>
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![Figure 4.](image-url)
for the unclassified group was 22.1 ± 7.0 IU/l, significantly higher ($P < 0.05$) than mean LH values in the low frequency, low frequency/low amplitude, and apulsatate groups (mean LH = 5.7 ± 1.4 IU/l, 3.6 ± 0.7 IU/l, and 5.5 ± 2.8 IU/l for low frequency, low frequency/low amplitude, and apulsatate respectively).

**Association of aetiology and neuro-endocrine pattern**

Eating disorder and stress/weight loss aetiologies showed a trend toward association with a low frequency LH pulse pattern ($P = 0.06$), when compared with idiopathic aetiology. No association was seen between idiopathic aetiology and any particular pattern of LH secretion.

**Pregnancy follow-up**

Pregnancy follow-up data was available for 26 subjects. Twenty-two subjects attempted pregnancy, and 21 were successful in conceiving and carrying at least one pregnancy to term. Eighteen subjects underwent ovulation induction including clomiphene citrate, pulsatile GnRH, or gonadotrophin therapy to conceive their first children. Three subjects recovered from HA prior to attempting conception, and were able to conceive their first children spontaneously. Four subjects who resumed menstrual function following their first pregnancies later went on to conceive spontaneously.

Seven of the 18 subjects (39%) who underwent ovulation induction achieved menstrual recovery following a successful pregnancy. Five recoveries were associated with sustained weight gains in previously underweight subjects. Two recoveries, which occurred in normal or overweight subjects, were not associated with weight gain.

**Discussion**

This longitudinal follow-up study of HA patients indicates that aetiology at the time of presentation predicts subsequent recovery of menstrual function. Weight loss, either alone or in the context of an eating disorder, was associated with HA development in 71% of our population, even when subjects remained within a normal range of weight for height. This is consistent with previous work indicating that a weight loss of ~10% of body weight in 1 year can cause amenorrhoea, regardless of premorbid weight (Nakamura et al., 1985). Recent research suggests that the process of dietary restriction itself may affect ovulation. Among normal weight women, ovulatory dysfunction was significantly correlated with dieting severity and decreased intake of dietary fat (Schweiger et al., 1992; Rock et al., 1996), and case-control research showed a higher fibre and lower fat intake in amenorrhoeic women than in normal controls, despite a similar overall caloric intake (Laughlin et al., 1998). Furthermore, caloric deprivation in normal volunteers has been shown to disrupt menstrual cycling both during weight loss and for some time following weight restoration (Pirke et al., 1985), with increased disruption on vegetarian versus meat-containing diets (Pirke et al., 1986).

The reasons often given by patients to explain voluntary weight loss are health and cosmetic improvement, but recent work points to a higher level of eating pathology in amenorrhoeic dieters than previously suspected. Several studies have reported higher scores on scales of eating disordered behaviour accompanying dietary restriction in women with HA (Warren et al., 1994; Laughlin et al., 1998). Measures of eating disordered behaviour were not obtained in our population at the time of diagnosis. However, the discovery that 54% of our population had a recent or remote history of an eating disorder, although none felt that she had an active eating disorder at the time of baseline study, raises the issue of hidden nutritional contributions to HA. Because correcting nutritional insults and pathological eating behaviour in the HA population has important prognostic implications, clinicians should seek evidence of subtle eating pathology in all patients presenting with HA.

In this study, 71% of women who developed HA following weight loss, an eating disorder, or stress recovered normal menstrual function, while only 29% of women with idiopathic HA recovered. Reversal of inciting conditions (weight loss, eating disorder, stress) occurred prior to menstrual resumption in all subjects, and 83% of subjects who returned to baseline weight and psychological functioning resumed menstruating. Thirty-nine per cent of subjects who had a successful pregnancy resumed cycling shortly thereafter, slightly lower than previously published rates (Lewinthal et al., 1987). However, pregnancy was accompanied by sustained weight gain in all underweight subjects who resumed cycling, which may indicate that weight recovery is necessary for pregnancy-associated menstrual recovery in underweight subjects. We found a higher rate of menstrual recovery following weight gain (78%) than previously reported rates, which ranged from 33–68% (Nakamura et al., 1985; Golden et al., 1997). The reason may be the longer duration of follow-up in the current study, as the mean duration of amenorrhoea in our population was 7.5 ± 1.2 years, and follow-up in other studies ranged from 1–3 years. Although recovery rates in this study were higher than previously reported, not all weight and psychologically recovered subjects resumed menstruating, indicating that reversal of inciting factors is necessary but not always sufficient for menstrual recovery in HA.

Underlying physiological differences may interplay with environmental insults in the development of and recovery from HA. The rate of prior menstrual dysfunction in our HA patients was 39%, higher than rates found in previous work (10–20%), and quite different from the insignificant rates of menstrual dysfunction seen in women who became amenorrhoeic secondary to other medical conditions (Reindollar et al., 1986). However, recovery rates did not differ between women with oligomenorrhoea compared with women who had normal menarche. Women with primary amenorrhoea showed a trend toward lower recovery rates, the significance of which might be better determined with larger study groups.

LH pulse patterns ranging from a complete absence of LH pulsations to normal-appearing patterns of secretion were not associated with statistically different rates of recovery. This may imply that the majority of abnormalities represent different time points in a single illness, rather than different illnesses. Previous work has shown that single individuals may manifest distinct patterns of LH secretion when studied at different time points during their illnesses without any associated clinical...
change or menstrual resumption (Reame et al., 1985; Perkins et al., 1999).

A decreased frequency of LH pulsations, the most frequently described abnormality in this population, was associated with eating disorder and stress/weight loss aetologies. This is consistent with previous work demonstrating an association between decreased LH pulse frequency and weight loss-related HA (Khoury et al., 1987; Berga et al., 1991), as well as work demonstrating that strict dieting decreases the frequency of LH pulsations in normal volunteers (Pirke et al., 1989).

This study had several limitations. Because it was a retrospective study, all dates, measurements, and attributions are based on subjects' recollections. However, the retrospective data obtained in interviews correlated well with both questionnaire data and with information from hospital records obtained at the time of presentation. The relatively low rate of follow-up (62%) introduces the possibility of selection bias. However, participating subjects did not differ from non-participating subjects in age at amenorrhea, duration of amenorrhea at presentation, or BMI. Finally, the small sample sizes may mask the prognostic significance of certain variables.

Despite its limitations, this study provides insight into the common aetiology and predictors of recovery in HA. Aetiology at the time of presentation is the most important predictor of menstrual recovery, with idiopathic HA conferring a worse prognosis. The most common aetiological factor is weight loss, either alone or with concurrent psychological factors. In stress, weight loss, or eating disorder-related HA, rates of recovery can exceed 80% when precipitating factors are reversed. Reversal of precipitating factors in these cases appears to be necessary but not sufficient for recovery. HA in women who present without precipitating factors may represent a different disorder, as recovery rates were <30% and there was no association with decreased frequency of LH pulsations. Further work is needed to elucidate potential genetic differences underlying the spectrum of HA.

References


Predictors of recovery in HA


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