Predictors of Resumption of Menses in Anorexia Nervosa: A 4-Year Longitudinal Study

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ABSTRACT

Objective: Amenorrhea is a disabling medical consequence of anorexia nervosa (AN); therefore, resumption of menses (ROM) represents an important goal in the treatment for these patients. The aim of the present study was to evaluate possible clinical, psychopathological, and biological predictors of ROM, including age, body mass index (BMI), AN subtype, childhood abuse, duration of illness, general and eating disorder (ED)–specific psychopathology, and sex hormones.

Methods: Fifty amenorrheic patients with AN were enrolled. Baseline clinical data and information on childhood abuse were collected. Questionnaires to evaluate general and ED-specific psychopathology were administered, and blood samples were drawn. All patients received treatment as usual and underwent regular follow-up visits for 4 years or until ROM. Time to ROM, BMI at last evaluation, and data regarding diagnostic crossover into bulimia nervosa were collected.

Results: Twenty-nine (58.0%) patients recovered menses. Diagnostic crossover was associated with a higher probability of ROM (odds ratio = 10.3, $p = .030$). Time-to-event analysis showed that a shorter duration of illness ($\chi^2(1) = 11.00$, $p = .001$), binge-eating/purging subtype ($\chi^2(1) = 7.01$, $p = .008$), and history of childhood abuse ($\chi^2(1) = 4.03$, $p = .045$) were associated with an earlier ROM. Furthermore, higher baseline ED-specific psychopathology was associated with a reduced likelihood for ROM, whereas higher general psychopathology and follicle-stimulating hormone levels predicted an earlier ROM (all, $p < .050$). Age, BMI, luteinizing hormone, and estrogen hematic levels had no predictive value with respect to ROM.

Conclusions: The present study provides data in support of an integrated model, emphasizing the importance of duration of illness, childhood abuse, and psychopathological characteristics of amenorrheic patients with AN in predicting ROM.

Key words: menses resumption, anorexia nervosa, childhood abuse, diagnostic crossover, sex hormones.

INTRODUCTION

Anorexia nervosa (AN) is a severe eating disorder (ED) characterized by food restriction, underweight, and an excessive importance attributed to body shape and weight (1). Two AN subcategories—AN restricting type (AN-r) and AN binge-eating/purging type (AN-bp)—are defined on the basis of the presence/absence of binge eating and purging behaviors (1).

AN is associated with several medical complications, and among these, amenorrhea is one of the most represented, with an estimated prevalence of 66% to 85% (2,3). The mechanism underlying amenorrhea in patients with AN is thought to be a functional hypogonadotropic hypogonadism (2). Considering that amenorrhea can precede weight loss and often persists after weight restoration (4–8), it seems that other factors could be involved in its onset and maintenance, besides pathological underweight. Among clinical variables, impaired body composition, starvation, stress, excessive physical exercise, and psychopathology have been considered (5,9–11). Given the severe consequences associated with persistent amenorrhea (12), resumption of menses (ROM) is an important therapeutic goal and it is considered a marker of recovery both in medical and psychopathological terms (13,14). Thus, the identification of prognostic factors for ROM is of considerable clinical interest.

Few prospective studies, with limited duration of follow-up, are available on this topic, often reporting conflicting results. In particular, duration of illness and psychopathological measures were shown to be associated or not with the time of ROM (8,15). Only a single research study considered AN subtype in studying ROM but failed to include it as a predictor (15). Regarding endocrinological and anthropometric features, previous studies demonstrated that lower levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) at baseline predicted a lower

AN = anorexia nervosa, **AN-bp** = anorexia nervosa binge-eating/purging type, **AN-r** = anorexia nervosa restricting type, **BMI** = body mass index, **CBT-E** = enhanced cognitive-behavioral therapy, **CI** = confidence interval, **ED** = eating disorder, **EDE-Q** = Eating Disorder Examination Questionnaire, **FSH** = follicle-stimulating hormone, **LH** = luteinizing hormone, **ROM** = resumption of menses, **SCL-90-R** = Symptom Checklist-90—Revised

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probability of ROM (8,16), whereas baseline body mass index (BMI) and estradiol were not associated with ROM (8,17). (18).

Furthermore, besides diagnostic categories, it has been postulated that within EDs, individuals reporting childhood abuse might represent a distinct subpopulation in terms of psychiatric and medical comorbidity and of long-term outcome (18). Indeed, they show a worse response to treatments and higher levels of diagnostic crossover, which consists in the transition to a different ED from the original one (18). Finally, patients with AN reporting childhood abuse seem to have distinct neuroendocrinological alterations as compared with the other patients (19,20). Therefore, although none of the available studies ever considered its role, childhood abuse could also be considered a plausible predictor of ROM, in addition to the factors already considered by the existing literature.

In light of the aforementioned considerations, the present study proposed an integrated model for predicting ROM in patients with AN. Multiple clinical, psychopathological, and biological prognostic factors for ROM were evaluated, including age, BMI, AN subtype, childhood abuse, duration of illness, general and ED specific psychopathology, and sex hormones, adopting both univariate and multivariate time-to-event analyses.

METHODS

The present study was a longitudinal observation with a 4-year follow-up conducted at the Clinic for Eating Disorders of the Psychiatric Unit of the University of Florence, Italy, between 2014 and 2019. All participants were adequately informed about the study and signed a consent form. The study protocol was approved by the ethics committee of the local institution (Comitato Etico Regionale per la Sperimentazione Clinica della Regione Toscana, sezione Area Vasta Centro).

Participants

The inclusion criteria were as follows: female sex, age between 18 and 40 years, current diagnosis of AN according to Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) (*DSM-5*) criteria, and presence of amenorrhea. Exclusion criteria included the following: relevant gynecological issues (e.g., endometriosis and diagnosis of polycystic ovary syndrome), pregnancy, comorbid psychotic disorder, bipolar I disorder, illiteracy, intellectual disability, severe medical conditions precluding treatment in an outpatient context, current use of oral contraceptives, or any other medications that can influence menstrual cycle.

Of the 91 patients with AN consecutively referred, 4 individuals declined to participate and 8 were excluded (2 comorbid bipolar I disorder, 3 severe medical conditions, 3 comorbid endometriosis).

Study Protocol

All patients recruited received treatment as usual, which included individual enhanced cognitive-behavioral therapy (CBT-E) for at least 40 weeks and regular dietetic evaluations in the context of day-hospital.

All patients carried out regular follow-ups every 3 months, in accordance with the normal clinical practice of the facility, during which full psychiatric evaluations were carried out by specialists, and data regarding menstrual status, weight, current therapy, and diagnosis were collected. Time to ROM, BMI at last evaluation, comorbid psychiatric disorders (according to *DSM-5* criteria), and data regarding diagnostic crossover were noted, the latter defined as meeting the criteria for a different ED than the original one (in this case AN), whereas the criteria for AN are no longer met.

Patients who started oral contraceptives or any other medications that could influence menses during the period of the study were considered lost to follow-up and were excluded from all statistical analyses.

Assessment and Measures

Both the initial and the follow-up evaluations were performed by two expert psychiatrists (G.C. and V.R.) through a face-to-face interview, collecting sociodemographic, pharmacological, and clinical data, including information on emotional, physical, or sexual abuse, defined in accordance with the *DSM-5* (1). Anthropometric measurements were made using standard calibrated instruments. At the time of enrollment, all participants were asked to complete two self-administered questionnaires:

- Symptom Checklist-90—Revised (SCL-90-R) (21), for the evaluation of general psychopathology, which includes a global severity index, obtainable from the average of all items. This scale showed an excellent internal consistency in our sample (Cronbach $\alpha = .98$).
- Eating Disorder Examination Questionnaire (EDE-Q) (22), for the evaluation of ED-specific psychopathology. It comprises a total score and four subscales measuring different features of EDs: dietary restraint, eating concern, weight concern, and shape concern. The internal consistency in our sample was excellent (Cronbach $\alpha = .92$).

Blood samples were drawn in the morning for determination of FSH, LH, and estradiol levels (electrochemiluminescence immunoassay; COBAS 600 [Roche Diagnostics, Basel, Switzerland]; the intra-assay and interassay coefficients of variation were 2.0% and 3.0% for FSH, 1.2% and 1.6% for LH, and 2.6% and 3.6% for estradiol).

Statistical Analysis

Comparisons between groups were performed by means of independent-samples t test and χ^2 test, whereas analysis of covariance was used to test for between-group differences while adjusting for baseline age and BMI. Logistic regression analysis was performed to evaluate the association between diagnostic crossover or psychiatric comorbidity at follow-up and ROM, adjusting for baseline age and BMI.

Maximally selected rank statistics were used to dichotomize the duration of illness to obtain a clinically useful parameter with the highest prognostic value for ROM. The Kaplan-Meier method (23) was used to estimate the likelihood for ROM associated with different durations of illness, AN subtypes, and childhood abuse. The Cox proportional hazards regression model (24) was used to assess the effect of all clinical, psychopathological, and biological variables on time to ROM. Given the limited sample size, the number of variables in the model was minimized by using the forward stepwise selection on all predictors that according to the *a priori* hypothesis could influence time to ROM. A likelihood ratio selection method was used, with a threshold for the probability of entry equal to .05. Of the 10 initial predictors, 6 were retained using this method (AN subtype, history of childhood abuse, duration of illness, EDE-Q, SCL-90-R, FSH) and 4 were excluded (age, BMI, LH, estradiol) from the final model. In all time-to-event analyses, ROM was considered the event of interest. All statistical analyses were conducted two-tailed. For the main outcome (i.e., time-to-event analyses) only patients reporting all data were included, whereas for secondary outcomes, a maximum of four missing values was observed for each analysis, which were managed with the pairwise deletion approach.

Maximally selected rank statistics were performed through the "maxstat" package (25) for R (26). The other analyses were performed using IBM SPSS Statistics version 25 (27).

RESULTS

Characteristics of the Sample

Of the 79 patients recruited who completed the baseline assessment, 29 were lost to follow-up (13 were not able to perform follow-up visits, 12 dropped out, 4 started hormonal therapy). These individuals did not differ from the rest of the sample regarding age, BMI, and psychopathological measures.

The final sample consisted of 50 patients with AN and amenorrhea, 35 AN-r and 15 AN-bp; 14 (28.0%) patients reported physical or sexual abuse in their childhood. Twenty-nine (58.0%) recovered menstrual cycle within the follow-up period (mean time to ROM = 18.8 [14.9] months). The proportion of patients with ROM was significantly greater among AN-bp as compared with AN-r patients (80.0% versus 48.6%, $\chi^2(1) = 4.26$, $p = .039$). Diagnostic crossover into bulimia nervosa was observed in 19 (38.0%) patients, and it was associated with a higher likelihood for ROM ($\chi^2(3) = 11.47$, $p = .009$; odds ratio = 10.3, $p = .030$). However, no significant difference in BMI at ROM was found between patients who experienced diagnostic crossover and those who did not (18.43 [1.83] versus 17.64 [2.63] kg/m^2, $p = .26$). A comorbid depressive or anxious disorder was detected in 8 (16.0%) participants at the last follow-up evaluation; psychiatric comorbidity was not associated with a variation in the likelihood for ROM ($\chi^2(3) = 11.16$, $p = .011$; odds ratio = 0.20, $p = .15$).

Table 1 shows the baseline characteristics of the sample, divided by diagnostic subtype and ROM, together with the results of comparisons between groups. AN-bp patients differed from AN-r patients in terms of longer duration of illness (Table 1). Furthermore, patients who recovered menstruations were on average younger and had higher BMI at baseline as compared with patients who never recovered menses during follow-up (Table 1). Patients who recovered menstruations showed a higher BMI at the last evaluation (18.72 [1.33] versus 16.32 [2.52] kg/m^2, $p < .001$).

Time-to-Event Analysis

Maximally selected rank statistics selected a 5-year cutoff point as a statistically significant threshold to maximize the prognostic value of duration of illness for ROM; consequently, the sample was divided into patients with a short (<5 years: "short duration of illness," $n = 26$) or long (≥5 years: "long duration of illness," $n = 24$) duration of illness.

Patients with short duration of illness had a mean time to ROM of 22.6 months (95% confidence interval [CI] = 15.4–29.9 months) and a median time of 15.1 months (95% CI = 5.8–24.3 months), which was less than that in patients with long duration of illness (mean time = 40.3 months; 95% CI = 34.9–45.6 months); the median time for the latter group was not calculable because the median time-to-event was not reached. The distributions of event times for the two groups were significantly different (Figure 1A).

The same analysis was performed with AN subtype as a between-subject factor. AN-r patients had a longer mean time to ROM (35.6 months, 95% CI = 29.7–41.5 months) than did AN-bp patients (20.5 months, 95% CI = 12.5–28.4 months). The median time was calculable only for the binge-purging subgroup (15.1 months, 95% CI = 5.5–24.6 months). The time-to-event distributions for the two subtypes were significantly different (Figure 1B).

A similar analysis was performed using the presence of childhood abuse as a between-subject factor. Patients with childhood abuse had a shorter mean time to ROM (26.0 months, 95% CI = 15.7–36.4 months) than did those without (35.0 months, 95% CI = 29.0–41.1 months); the median time was calculable only for the subgroup with a history of trauma (20.1 months, 95% CI = 9.8–30.4 months). The distributions of event times were significantly different (Figure 1C).

A multivariate Cox regression model was performed to evaluate the prognostic role of baseline covariates on ROM (Table 2). Belonging to AN-bp subtype and having a history of childhood abuse predicted a higher probability of ROM, whereas a longer

TABLE 1. Characteristics of the Sample at Baseline, Reported as Mean (SD), Together With the Results of Comparisons Between Groups Performed by Independent-Samples *t*-Tests (for Age and BMI) and ANCOVAs (Correcting for Age and BMI)

	AN-r ($n = 15$)	AN-bp ($n = 35$)	*t* or Age and BMI-Adjusted *F*	Patients Not Recovering Menses ($n = 21$)	Patients Recovering Menses ($n = 29$)	*t* or Age and BMI-Adjusted *F*
Age, y	24.60 (7.01)	23.40 (6.20)	0.57	27.52 (7.59)	21.86 (4.93)	2.99**
Baseline BMI, kg/m^2	15.80 (1.54)	16.56 (1.70)	−1.49	15.45 (1.18)	16.46 (1.77)	−2.20*
Duration of illness, y	5.78 (6.60)	7.42 (6.23)	7.51**	8.82 (7.39)	4.19 (4.88)	0.25
EDE-Q dietary restraint	2.86 (1.98)	4.10 (1.92)	2.09	3.17 (2.13)	3.26 (1.99)	0.28
EDE-Q eating concern	2.29 (1.60)	3.37 (1.70)	3.10	2.57 (1.56)	2.64 (1.79)	0.09
EDE-Q weight concern	2.53 (1.62)	3.70 (1.76)	2.73	2.91 (1.58)	2.86 (1.86)	0.52
EDE-Q shape concern	3.04 (1.69)	4.27 (1.90)	2.63	3.32 (1.80)	3.46 (1.88)	0.25
EDE-Q total score	2.68 (1.58)	3.86 (1.73)	2.99	2.99 (1.63)	3.06 (1.77)	0.30
SCL-90-R GSI	1.35 (0.76)	1.81 (0.48)	2.94	1.36 (0.73)	1.59 (0.70)	0.23
FSH, mIU/ml	3.74 (2.67)	4.85 (4.14)	0.59	3.18 (2.52)	4.99 (3.62)	1.30
LH, mIU/ml	1.71 (2.45)	2.89 (4.10)	0.39	1.66 (2.80)	2.52 (3.37)	0.08
Estradiol, nmol/L	0.11 (0.10)	0.09 (0.04)	0.71	0.08 (0.06)	0.12 (0.11)	1.02

SD = standard deviation; BMI = body mass index; ANCOVAs = analyses of covariance; AN-r = anorexia nervosa restricting type; AN-bp = anorexia nervosa binge-eating/purging type; EDE-Q = Eating Disorder Examination Questionnaire; SCL-90-R GSI = Symptom Checklist-90—Revised Global Severity Index; FSH = follicle-stimulating hormone; LH = luteinizing hormone.

t and *F* values are shown alongside their statistical significance.

* $p < .050$.

** $p < .010$.

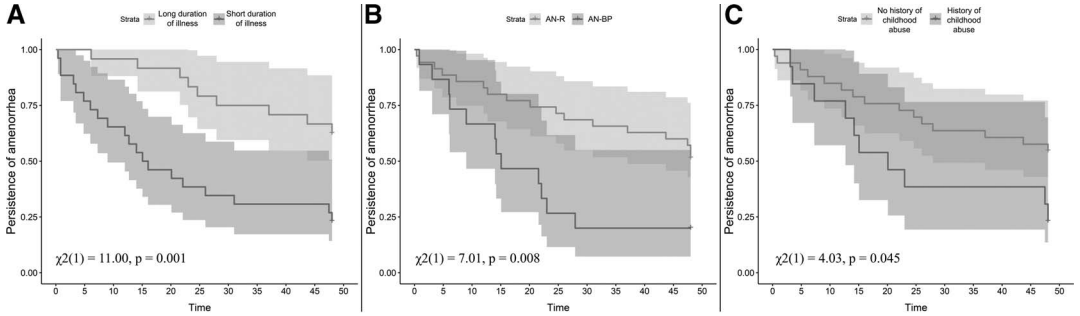

FIGURE 1. Kaplan-Meier curves for the effect of duration of illness (A), anorexia nervosa subtype (B), and history of childhood abuse (C) on resumption of menses together with the results of the log-rank tests for differences in the distributions of event times. Duration of illness was dichotomized using a cutoff of 5 years. AN-R = anorexia nervosa restricting type; AN-BP = anorexia nervosa binge-eating/purging type.

duration of illness negatively influenced it (Table 2). Considering psychopathological measures, higher baseline EDE-Q scores were associated with a reduced likelihood for ROM, whereas higher levels of general psychopathology were associated with an earlier ROM (Table 2). Furthermore, among considered hormones, only baseline FSH was associated with a higher likelihood for ROM (Table 2). Neither age nor BMI had a predictive value with respect to ROM. The model was also tested, further reducing the number of variables (SCL-90-R and FSH were removed); the results remained comparable to those reported in Table 2.

DISCUSSION

To the best of our knowledge, this is one of few studies assessing prognostic factors for ROM in AN including clinical, psychopathological, and biological variables into a comprehensive multivariate model, and the first evaluating the role of AN subtype and childhood abuse.

It is important to note that both in univariate and multivariate models a shorter duration of illness was associated with a better outcome in terms of ROM. More precisely, time-to-event curves showed that 5 years of illness was the discriminating value in determining a lengthening in the time of ROM. This result is in line with what reported by Copeland et al. (15) and with the well-known relationship between a longer duration of illness and a poorer outcome in AN (28). Thus, it underlines the importance of early diagnoses and interventions to ameliorate the outcome of these patients.

Considering those variables commonly associated with a worse prognosis in terms of ROM, according to the multivariate model, neither age nor BMI predicted the time of ROM. This seems to confirm that baseline BMI, per se, should not be considered as a predictor of ROM (8,17). The positive prognostic value of elevated baseline FSH levels is in line with previous literature (16). The lack of predictive value of the levels of estradiol was to be expected considering the uniformly low values found in the observed sample, and it is in line with previous findings (8). Even LH levels did not show an association with a variation in the time of ROM. It could be hypothesized that the relationship between LH and ROM previously observed by Golden et al. (8) was due to a confounding variable, possibly the FSH itself, and that the multivariate approach adopted in this study made it possible to separate the effect of the covariates. Furthermore, the present study confirmed the importance of core ED psychopathology as a marker of treatment resistance in AN (29,30), as patients with greater ED symptoms at baseline were less likely to recover menses at follow-up, even when adjusting for severity of underweight.

On the other hand, quite surprisingly, it was observed that patients with childhood abuse showed an earlier ROM as compared with the other participants. This result could be interpreted considering that traumatic eco-phenotype has been associated with a nonmonophasic disease trajectory, with higher rates of diagnostic

TABLE 2. Cox Proportional Hazard Regression Multivariate Analysis for the Resumption of Menses

	Coefficient	HR	95% CI	*p*
AN subtype	2.29	▲9.83	2.10–45.97	.004
History of childhood abuse	1.45	▲4.26	1.17–15.48	.028
Duration of illness, y	−0.28	▼0.76	0.64–0.90	.002
EDE-Q total score	−1.05	▼0.35	0.18–0.68	.002
SCL-90-R GSI	2.10	▲8.17	2.07–32.32	.003
FSH, mIU/ml	0.26	▲1.30	1.06–1.58	.010

All variables were collected at baseline and were inserted in the model as predictors of resumption of menses. For AN subtype, the reference category was the restricting type (as opposed to the binge-eating/purging type), whereas for history of childhood abuse, the reference category was absence of abuse.

▲ indicates factor significantly associated with higher likelihood for resumption of menses; ▼ indicates factor significantly associated with reduced likelihood for resumption of menses.

HR = hazard ratio; CI = confidence interval; AN = anorexia nervosa; EDE-Q = Eating Disorder Examination Questionnaire; SCL-90-R GSI = Symptom Checklist-90—Revised Global Severity Index; FSH = follicle-stimulating hormone.

crossover (18). It could be hypothesized that traumatized individuals could represent a separate group of patients with AN in whom ROM may not represent a marker of recovery from the ED, but rather a marker of weight recovery induced by the transition to a new phase of disease. This hypothesis seems to be confirmed by the fact that in our sample diagnostic crossover was associated with ROM. Moreover, AN-bp subtype and higher levels of general psychopathology, features that are typically associated with diagnostic crossover and with a history of abuse (29,31), predicted an earlier ROM.

All participants in this study received individual CBT-E, which was preferred over other psychotherapy models because of its transdiagnostic approach to the treatment of EDs, addressing the common underlying mechanisms, regardless diagnostic categories (22). In particular, the advantage represented by CBT-E is that it is generally targeted to both ED-specific psychopathology (body shape and weight concerns, weight recovery, disruption of maladaptive behavior) and other common psychopathological features (e.g., emotion dysregulation and perfectionism). Furthermore, multidisciplinary framework adopted for this study (including psychiatrist, dieticians, and internists) allowed for addressing several different factors possibly interfering with ROM.

In conclusion, these results underline the importance of considering duration of illness, childhood abuse, and psychopathological characteristics of amenorrheic patients with AN when predicting ROM rather than merely age and BMI. Considering all these factors may provide an integrated view, allowing clinicians to estimate more accurately the probability of menses recovery when visiting patients at baseline.

The strength of the present study is represented by the long duration of follow-up. However, it presents some limitations. First, body composition measures were not collected. Second, only self-administered questionnaires were collected, and no psychometric questionnaire was administrated at follow-up. Finally, although the dropout and loss to follow-up rates were considered acceptable for this study, they still represent a limitation.

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