

## Mini-Review

# Menstrual Dysfunction in Anorexia Nervosa

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**Abstract.** Amenorrhea is a hallmark sign of anorexia nervosa. Its cause is multifactorial and its resolution necessitates treatment of the underlying eating disorder. The neuroendocrine changes associated with menstrual abnormalities in underweight and weight recovered anorexia nervosa, recent research on osteopenia, and treatment recommendations are addressed.

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**Key Words.** Anorexia nervosa—Amenorrhea—Neuroendocrine abnormalities

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### Introduction

Anorexia nervosa affects 1% to 3% of adolescents and young adults in the United States.<sup>1,2</sup> Menstrual irregularities are often the presenting concern, placing the gynecologic clinician in an advantageous position for accurate and timely diagnosis of the eating disorder. This article will review the pathophysiology of menstrual problems in patients with anorexia nervosa and update the reader on current treatment recommendations for associated osteopenia.

### Diagnosis

Amenorrhea is one of the four diagnostic criteria of anorexia nervosa (see Table 1).<sup>3</sup> In up to two thirds of patients, absence of menses precedes significant weight loss,<sup>4,5</sup> making initial diagnosis of the eating

disorder more difficult. Evaluation of amenorrhea in all patients must include thorough examination of exercise and nutritional habits. Body image should also be explored. The SCOFF questionnaire (see Table 2) is an easily administered screening tool for use in primary care settings which incorporates body image questions.<sup>6,7</sup> If a diagnosis of anorexia nervosa is suspected but still unclear after initial interview, mental health referral and further medical evaluation should occur simultaneously.

### Physical Examination

Physical examination of a patient with anorexia nervosa generally reveals bradycardia, hypothermia, dry skin, lanugo, and yellowing of the skin due to hypercarotenemia. Severe emaciation, as noted by the scaphoid abdomen and loss of subcutaneous fat in the extremities and trunk, may be overlooked if the patient is not examined in a gown. Submandibular adenopathy or parotid gland enlargement result from frequent emesis. A cardiac murmur may signify anemia or mitral valve prolapse, a reversible condition associated with loss of left ventricular mass noted in up to 37% of patients.<sup>8,9</sup> External genital examination typically reveals prepubertal-appearing vaginal mucosa secondary to hypoestrogenemia. In the patient with obvious weight loss, behaviors consistent with anorexia nervosa, and no history of sexual activity, a full pelvic examination for the evaluation of amenorrhea is unnecessary.

### Laboratory Evaluation

Laboratory evaluation in the patient with anorexia identifies medical complications of malnutrition and should include a complete blood cell count, electrolytes, blood urea nitrogen, creatinine, and liver

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*Synopsis:* A review of recent research in anorexia nervosa regarding osteopenia and neuroendocrine changes associated with menstrual abnormalities in underweight and weight recovery, with diagnosis and management options is provided.

**Table 1.** Diagnostic Criteria for Anorexia Nervosa<sup>a</sup>

1. Refusal to maintain body weight at or above a minimally normal weight for height and age.
2. Intense fear of gaining weight or being fat, even though underweight.
3. Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight.
4. Amenorrhea
  - ◆ Restrictive subtype: the person has not regularly engaged in binge-eating or purging behavior (weight is mainly controlled by restricting oral intake)
  - ◆ Binge-eating/purging subtype: patient regularly engages in binge eating and/or purging (e.g. self-induced vomiting, misuse of laxatives)

<sup>a</sup>From DSM-IV, American Psychiatric Association<sup>3</sup>.

function tests. Luteinizing hormone (LH), follicle stimulating hormone (FSH), and serum estradiol levels are all low in women with anorexia nervosa. Prolactin and thyroid stimulating hormone (TSH) are normal (Table 3).<sup>4,10</sup> Assessment of the hypothalamic-pituitary-ovarian (HPO) axis need occur only in cases where etiology of amenorrhea is unclear after history and physical. Urine pregnancy test is indicated for sexually active females or those who reveal sexual abuse.

### Hypothalamic-Pituitary-Ovarian Axis

The hypothalamic hypogonadism responsible for amenorrhea in anorexia nervosa is related to a prepubertal pulsatile secretion pattern of LH, seen even in those teens who previously had regular monthly menstrual cycles.<sup>11,12</sup> Early studies demonstrate that administration of clomiphene or exogenous estrogen fail to increase gonadotropin secretion, pointing to a dysfunctional hypothalamic response to the normal positive feedback mechanism of estrogen.<sup>13,14</sup>

### Hypothalamic-Pituitary-Adrenal Axis

Further evidence of hypothalamic dysfunction is seen with abnormal cortisol regulation. Underweight patients with anorexia nervosa have decreased dehydroepiandrosterone sulfate (DHEAS) levels,<sup>15</sup> elevated levels of evening total and free serum cortisol, and

**Table 2.** The SCOFF Questionnaire<sup>a</sup>

- Do you make yourself Sick because you feel uncomfortably full?
- Do you worry you have lost Control over how much you eat?
- Have you recently lost more than One stone in a 3 month period?<sup>b</sup>
- Do you believe yourself to be Fat when others say you are too thin?
- would you say that Food dominates your life?

Scoring: one point for every "yes"; score of  $\geq 2$  suggests an eating disorder.

<sup>a</sup>From Morgan, JF, Reid F., Lacey JH.<sup>6</sup>

<sup>b</sup>One stone  $\approx$  14 pounds or 6 kg.

**Table 3.** Hormone Values in Anorexia Nervosa

Low	Normal	High
FSH	TSH	Serum total cortisol
LH	Prolactin	Serum free cortisol
Estradiol	ACTH	24-hour urinary free cortisol
Leptin		
IGF-1		
DHEAS		

higher 24-hr urinary free cortisol excretion levels when compared to control subjects. Despite this, serum adrenocorticotrophic hormone (ACTH) levels are normal. Administration of dexamethasone fails to suppress hypercortisolemia. Administration of corticotropin-releasing hormone (CRH) demonstrates an exaggerated cortisol production response relative to lower than expected ACTH levels. With restoration of body weight, hypercortisolemia resolves, yet a blunted ACTH response to CRH persists for several months. Hypercortisolemia in patients with anorexia nervosa appears to arise from a combination of excess secretion of CRH and a hyper-responsive adrenal gland. Normalization of the hypothalamic-pituitary-adrenal axis occurs with long term weight recovery.<sup>16</sup>

### Leptin

Leptin is a protein hormone produced mainly by adipocytes. It is a key component in the regulation of energy balance and body composition, and its role in eating disorders is an area of much research. Leptin levels are highest in obese women, lowest in patients with anorexia nervosa. This is not directly due to the amount of functioning adipocytes, however. Leptin levels in healthy, menstruating, constitutionally thin women are higher than in anorexia patients. Moreover, leptin levels are correlated to both body mass index (BMI) and body fat in normal weight and lean menstruating women but not correlated in anorexia patients.<sup>17</sup>

A critical leptin level, below which amenorrhea is triggered, could serve as a biological protective mechanism during times of famine to safeguard against energy demanding reproductive function. In anorexia nervosa, however, normalization of leptin levels is not sufficient for return of menstrual function. Eumenorrheic and amenorrheic weight recovered anorectics have similar normal leptin levels but the latter persist with low estradiol and growth hormone levels.<sup>18</sup> One modulating factor may be insulin-like growth factor 1 (IGF-1). The low leptin levels in women with anorexia nervosa are significantly correlated to low IGF-1 levels, in contrast to constitutionally thin women with similar low leptin levels.<sup>17</sup> Nutritional status and IGF-1 level, and not simply leptin, may be the key factor in weight-loss related amenorrhea. Further research in this area is needed.

## Exercise and the Female Athlete Triad

Menstrual irregularities associated with excessive exercise in non eating-disordered athletes are due to hypothalamic dysfunction with a decrease in the pulse frequency of gonadotropin-releasing hormone (GnRH), leading to low levels of FSH, LH, and estradiol.<sup>19</sup> Repeated administration of exogenous GnRH results in normalization of LH secretion patterns in anorectics, but demonstrates an exaggerated response in non eating-disordered athletes suggesting a different mechanism for athletic amenorrhea.<sup>20</sup>

The female athlete triad marks a subset of athletes with three co-existent medical concerns: disordered eating, amenorrhea, and osteoporosis. Athletes do not need to meet full criteria from Diagnostic and Statistical Manual of Mental Disorders, 4th ed, (DSM-IV) for an eating disorder, but may demonstrate any combination of restrictive eating, binge eating, or purging behaviors. Unhealthy eating is often coupled to obsessive exercise or exercise in excess of that required for successful sport participation.

## Menstrual Irregularities in Weight Recovered Anorexia

The return of menses is directly correlated with restoration of an individualized healthy body weight. No relationship has been found between return of menses and percent body fat or BMI.<sup>21,22</sup> Over 85% of patients will have spontaneous return to menses within 6 months of achieving a weight 90% of their ideal body weight.<sup>22</sup>

Persistent amenorrhea may reflect improper terminology in that these patients are not truly “weight recovered” but merely of weight in normative ranges. Amenorrheic patients have significantly lower mean weights, lower weight-to-height ratios, and smaller ovarian volumes than menstruating patients in recovery.<sup>23</sup> Amenorrheic patients do not differ in age of menarche, duration of illness, or amount of weight initially lost.<sup>22</sup>

Once weight is normalized, FSH, LH, and progesterone levels normalize, yet amenorrheic patients have estradiol and leptin levels lower than menstruating control patients.<sup>24</sup> Hypoestrogenemia correlates to persistent ovarian dysfunction. Key and colleagues found only 41% of adolescents recovering from anorexia nervosa will have a mature ultrasonographic appearance of their ovaries and uterus at a weight-to-height ratio of 95%.<sup>25</sup> Ultrasonographic appearance of the ovary in anorexia nervosa passes through three stages. While underweight and hypoestrogenemic, the ovaries are small and amorphous. With weight gain, small multifollicular cysts appear. Return to normal

morphology and appearance of a dominant ovarian follicle correlates to premorbid weight, and not simply BMI.<sup>26</sup> Pelvic ultrasound conducted by an experienced ultrasonographer can be a useful adjunctive tool in discerning the appropriate final weight in persistently amenorrheic patients.

Psychological recovery may be as important as weight for return of menses. Weight recovered patients with persistent amenorrhea restrict fat intake more<sup>27</sup> and score higher on “anorexic” measurements such as preoccupation with the nutritional value of food and distorted perception of body depth than do menstruating peers.<sup>28</sup> Depression, a common dual diagnosis in anorexia nervosa patients,<sup>29</sup> has also been linked to amenorrhea.<sup>30</sup>

Long-term followup studies have shown no increased risk of infertility in those women who achieve a healthy weight and return of menses.<sup>31,32</sup> Pregnancy may trigger new body image concerns and clinicians should stay alert to signs of relapse into an active eating disorder.

## Bone Mineral Density

The decreased bone formation and increased resorption seen in anorexia nervosa are associated with high rates of osteopenia and osteoporosis.<sup>33</sup> Osteopenia, or reduced bone mass, has been shown in 44% to 92% of patients presenting with amenorrhea less than 24 months duration.<sup>34–36</sup> Risk of osteoporosis, consisting of decreased bone mass, decreased bone strength, and pathologic fracture, correlates best with duration of illness and the patient’s body mass index.<sup>37–41</sup> Bone mineral density (BMD) does not correlate with duration of secondary amenorrhea, dietary calcium intake, amount of exercise, or use of oral contraceptives. Although some cross-sectional studies suggest normalization of BMD occurs in weight recovered women,<sup>38,42,43</sup> recent prospective studies provide evidence that osteopenia improves, but does not resolve, with weight gain.<sup>15,36,40</sup>

Treatment of anorexia associated osteopenia is an area of much research. Cross-sectional studies,<sup>38</sup> retrospective studies,<sup>44</sup> and prospective studies<sup>36,40,45,46</sup> have all failed to show any positive association between hormone replacement therapy and bone mineral density. One recent prospective study demonstrated that administration of both oral contraceptives and recombinant human IGF-1 had a significant positive effect on bone mineral density while use of oral contraceptives alone was associated with continued bone loss. In addition, those subjects who received only IGF-1 injections demonstrated positive changes in BMD, but this effect was not as dramatic as the patients

in the combination group.<sup>47</sup> In another study, administration of oral DHEA correlated with increases in bone-specific alkaline phosphatase, a marker of bone formation, but did not result in significant improvement in BMD over a 12-month period.<sup>15</sup>

The benefit of using spontaneous return of menses as a marker of appropriate recovered weight must be balanced against the medically unsupported use of exogenous estrogen in the majority of cases. Although anorexics are anovulatory while underweight, with weight recovery undesired pregnancy may occur prior to resumption of regular menstrual cycles, which would be one indication for the use of oral contraceptives.

Amenorrhea is a common concern prompting young women to seek gynecologic evaluation. Medical providers should remain alert to the signs and symptoms of anorexia nervosa, voice their concerns without hesitation, and assist families in accessing appropriate interdisciplinary care with a mental health provider, registered dietitian, and experienced medical provider.<sup>1</sup> With early and aggressive treatment, weight recovery and an acceptable quality of life are possible for over 85% of young patients.<sup>48</sup>

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