Eating Disorders and Menstrual Dysfunction in Adolescents

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Menstrual dysfunction is a common feature of all eating disorders and results in significant medical complications. The etiology of menstrual dysfunction is multifaceted and the result of a complex interplay of many factors including weight loss, decreased body fat, hypoleptinemia, abnormal eating attitudes and behaviors, exercise, and psychological stressors. This chapter will review the prevalence of menstrual dysfunction in adolescents with eating disorders, its multifactorial etiology, the evidence-based pathophysiology, and the resulting complications to linear growth, pubertal development, bone mineral accretion, and cognitive function. Future research directions are identified that suggest opportunities to gain new insights into our understanding of the mechanisms and treatment of menstrual dysfunction in adolescents with eating disorders.

Key words: **eating disorders; anorexia nervosa; bulimia nervosa; adolescents; menarche; amenorrhea; oligomenorrhea; menstrual dysfunction; pubertal delay; hypothalamic hypogonadism**

Introduction

Eating disorders are complex illnesses causing significant morbidity and mortality.[1–5] When the onset of these disorders occurs in childhood or adolescence, delay of menarche, interruption of pubertal maturation, and menstrual cycle disturbances may occur. Menstrual dysfunction is a common clinical feature of all types of eating disorders.[6] The etiology, of menstrual dysfunction is complex, involving multiple factors such as weight loss, decreased body fat, hypoleptinemia, abnormal eating attitudes and behaviors, exercise, and psychological stressors. This chapter will review the prevalence of menstrual dysfunction in eating disorders, its multifactorial etiology, and the implications of menstrual dysfunction on growth and pubertal development, bone mineral accretion, and cognitive function.

Background

According to the *Diagnostic and Statistical Manual of Mental Disorders* (4th edition, text revision) (DSM-IV-TR),[7] eating disorders fall into one of three categories (Table 1): anorexia nervosa (AN), (OMIM %606788), bulimia nervosa (BN), (OMIM %607499), and eating disorder not otherwise specified (ED-NOS). Diagnosis can be challenging in children and adolescents as they often do not meet the strict diagnostic criteria outlined in the DSM-IV-TR.[8–10]

Anorexia Nervosa

Anorexia nervosa is the third most common chronic disease among adolescent females[9] and has a prevalence between 0.3–1.2%.[11,12] Patients with AN refuse to maintain a body weight that is consistent with health for someone of their gender, age, and height. In children and adolescents, this may manifest as failure to make expected weight gains. Patients also have an intense fear of gaining weight or becoming fat and a disturbance in the way in which they experience their body weight or shape. The final diagnostic criterion is amenorrhea, defined as the absence of at least three consecutive menstrual cycles in postmenarchal females. In addition, an adolescent is considered to have amenorrhea if her periods occur only following hormone administration (e.g., hormonal therapy). Because AN may occur in prepubertal girls, there is concern that the amenorrhea criterion limit the diagnosis of AN in children and younger adolescents.

The course of AN is often protracted.[2] Mortality due to AN is approximately 5.6% per decade; this is the highest mortality rate of any psychiatric disorder. Medical complications are common and AN can affect every organ system in the body.[4,5] Quality of life can also be significantly impaired, with higher rates

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TABLE 1. DSM-IV-TR classification of eating disorders[a]

Eating disorder	DSM-IV-TR criteria
Anorexia nervosa	A. Refusal to maintain body weight at or above a minimally normal weight for age and height (e.g., weight weight loss leading to maintenance of body weight <85% of that expected; or failure to make expected weight gain during period of growth, leading to weight <85% of that expected) B. Intense fear of gaining weight or becoming fat, even though underweight C. Disturbance in the way in which one's body weight or shape is experienced, undue influence of body body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight D. In postmenarchal females, amenorrhea, i.e., absence of at least three consecutive menstrual cycles. (A woman is considered to have amenorrhea if her periods occur only following hormone, e.g., estrogen, administration.) Specify type: Restricting Type: during the current episode of anorexia nervosa, the person has not regularly engaged in binge-eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas) Binge-Eating/Purging Type: during the current episode of anorexia nervosa, the person has regularly engaged in binge-eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas)
Bulimia nervosa	A. Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following: 1. Eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances 2. A sense of lack of control over eating during the episode (e.g., a feeling one cannot stop eating or control what or how much one is eating) B. Recurrent inappropriate compensatory behavior to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, enemas, or other medications; fasting; or excessive exercise C. The binge eating and inappropriate compensatory behaviors both occur, on average, at least twice a week for 3 months D. Self-evaluation is unduly influenced by body shape and weight E. The disturbance does not occur exclusively during episodes of anorexia nervosa Specify type: Purging Type: during the current episode of bulimia nervosa, the person has regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics, or enemas Nonpurging Type: during the current episode of bulimia nervosa, the person has used other inappropriate compensatory behaviors, such as fasting or excessive exercise, but has not regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics, or enemas
Eating disorder not otherwise specified	The Eating Disorder Not Otherwise Specified category is for disorders of eating that do not meet the criteria for any specific eating disorder. Examples include: 1. For females, all of the criteria for anorexia nervosa are met except that the individual has regular menses 2. All of the criteria for anorexia nervosa are met except that, despite significant weight loss, the individual's current weight is in the normal range 3. All of the criteria for bulimia nervosa are met except that the binge eating and inappropriate compensatory compensatory mechanisms occur at a frequency of less than twice a week or for a duration of less than 3 months 4. The regular use of inappropriate compensatory behaviors by an individual of normal body weight after eating eating small amounts of food (e.g., self-induced vomiting after the consumption of two cookies) 5. Repeatedly chewing and spitting out, but not swallowing, large amounts of food 6. Binge-eating disorder: recurrent episodes of binge eating in the absence of the regular use of inappropriate compensatory behaviors characteristic of bulimia nervosa

[a]Reprinted with permission from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*, Copyright 2000. American Psychiatric Association.

of social isolation, co-morbid psychiatric disorders, failure to complete educational goals, and unemployment.[3,13–19] Early intervention is crucial for a positive outcome.

Bulimia Nervosa

Bulimia nervosa has a prevalence of 1–5%.[1,11] Patients with BN engage in recurrent episodes of binge eating, characterized by eating a large amount of food

in a short period of time, while feeling out of control during this eating behavior. Binge eating episodes result in recurrent inappropriate compensatory behaviors to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, enemas, or other medications; fasting; or excessive exercise. Similar to AN, patients with BN are overly influenced by body weight and shape. Unlike patients with AN, patients with BN can be normal weight, overweight, or underweight.

BN is associated with a variable course, with many patients achieving a good outcome and others having a chronic and relapsing course.[20–24] Outcome studies in patients with BN report a mortality rate ranging from 0–1.1% and this varies with duration of follow-up.[13,20,21,23] The binge/purge symptoms of BN can result in medical complications as well as impairment in social, school, and work functioning.[3,13,20–24] BN is also associated with higher rates of co-morbid psychiatric disorders and substance abuse.[20–25]

Eating Disorder Not Otherwise Specified

The prevalence of eating disorder not otherwise specified (EDNOS) is less clear than that of AN and BN because of the heterogeneity of clinically significant eating disorders that fall into this category. EDNOS covers a range of clinically significant disordered eating behaviors (TABLE 1), including those that meet some, but not all the criteria for AN or BN, those that have atypical clinical features of AN and BN, and those that have binge-eating disorder. Because of the heterogeneity among patients diagnosed with EDNOS, up to 50–60% of children, adolescents, and young adults with eating disorders will fall into this diagnostic category.[8,26–29]

To date, there are no long-term outcome studies of adolescents or adults diagnosed with EDNOS. As a result, rates of mortality and morbidity in this group are largely unknown. Studies of adults with a diagnosis of EDNOS have shown that the psychopathology and degree of psychosocial impairment in this population closely resembles that of adults with AN and BN.[26–28,30] The reports of EDNOS are primarily focused on older adolescents and adults. Therefore, these findings cannot be generalized to all adolescents with EDNOS.

Eating Disorders and Menstrual Dysfunction

Amenorrhea is one of the four diagnostic criteria of AN.[7] However, many patients with BN and EDNOS also experience amenorrhea or oligomenorrhea.[6,31–37] Whether or not amenorrhea should be included as a diagnostic criterion for children and adolescents is a matter of great debate.[9,38] The absence of menstrual periods in early puberty and the physiologic irregular menstrual periods that normally occur after menarche, limit the application of this criterion in adolescents.[9] As well, there is a proportion of females who demonstrate all the signs and symptoms of AN, but continue to menstruate despite being severely undernourished and of low weight.[38]

Despite this ongoing debate, amenorrhea currently exists as part of the diagnostic criteria. Of significance, the onset of an eating disorder before, during, or after puberty can result in primary or secondary amenorrhea or oligomenorrhea.

Anorexia Nervosa

Amenorrhea associated with AN is thought to be secondary to hypothalamic dysfunction. The cause is unclear, but is associated with multiple factors including weight loss, decreased body fat, hypoleptinemia, abnormal eating attitudes and behaviors, exercise, and psychological stressors. These factors will be discussed in further detail below.

Hypothalamic-Pituitary-Ovarian Axis

Adolescents with AN have hypothalamic hypogonadism with impaired gonadotropin-releasing hormone (GnRH) secretion by the hypothalamus and low serum levels of luteinizing hormone (LH), follicular-stimulating hormone (FSH), and estradiol.[39–41] During healthy pubertal development, LH levels show a typical pattern of progression from prepuberty to adulthood.[42] Prepubertal children have low levels of LH, with minimal variation during the day and night. With the onset of puberty, there is an increase in LH secretion by the pituitary gland during sleep. As puberty progresses, LH secretion occurs both day and night, with LH secretion remaining greatest at night. By adulthood, there is episodic LH secretion of equal frequency and amplitude that occurs during waking and sleeping (FIG. 1). Reports have shown that adolescents with AN display a prepubertal or early pubertal pulsatile secretion pattern of LH. Boyar *et al.*[43] demonstrated age-inappropriate 24-hour LH secretion patterns in females ages 17 to 23 years with AN and primary or secondary amenorrhea (FIGS. 2 and 3). These findings suggest that females with AN have a regression of the hypothalamic-pituitary-ovarian axis, with an associated arrest in normal menstrual functioning.

Menstrual Function and Body Weight

The growing literature on the return of menstrual function in females with AN helps to explain in part

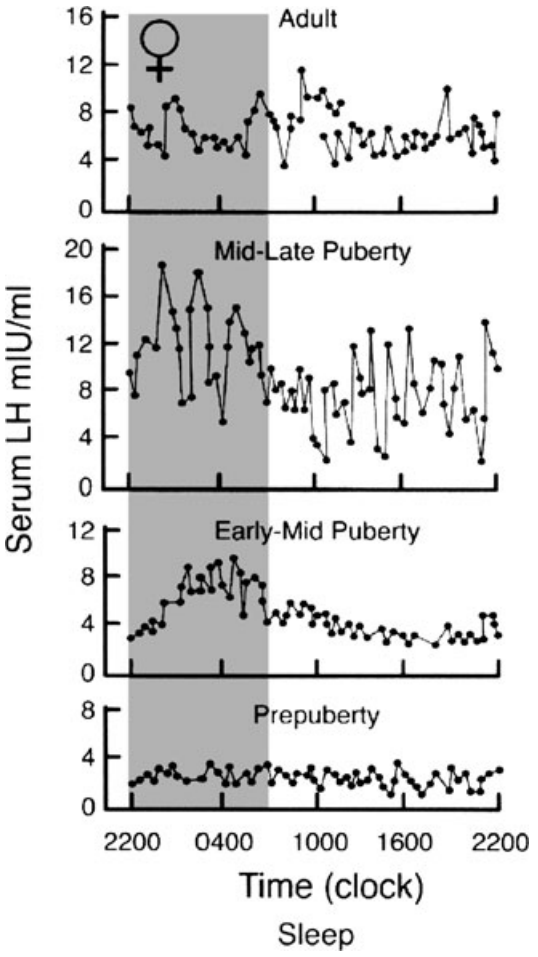

FIGURE 1. Progression of LH secretion pattern from prepuberty to adulthood. (From Ref. 42. Reprinted by permission.)

the relationship between the amenorrhea of AN and body weight. When reviewing this literature, it is important to keep in mind that the definition of "ideal body weight" (IBW) differs widely across studies, making the results difficult to compare.

Golden *et al.*[44] measured body weight, percent body fat using skinfold measurements, and serum LH, FSH and estradiol levels at baseline and every three months until return of menses in a cohort of adolescent girls with AN and secondary amenorrhea. Return of menses occurred at 90% of IBW (defined as the median weight for height and age using National Center for Health Statistics tables) in 86% of adolescents within 6 months of achieving this weight. The group reported that adolescents with secondary amenorrhea needed to be at a weight that was 2.05 kg greater than the weight at which they lost their menstrual period for menstruation to resume. The return of menses was also associated with a serum estradiol > 110 pmol/L. Finally, there was no significant difference in body weight, body mass index (BMI), and % body fat between patients who had a return of menstrual function with those who did not. A retrospective study by Shomento and Kreipe[45] found similar results, with the return of menses occurring at 92% of IBW.

Swenne[46] demonstrated that the return of menses was achieved when patients reached a weight consistent with their prepubertal growth trajectory. This group suggested that target weight should be based on a patient's individual pre-illness growth curve percentile (i.e., their inborn genetic potential) as opposed to population norms of weight for height since there are a proportion of adolescent females who need to achieve a weight or BMI above the population average in order to menstruate.

The use of pelvic ultrasound has been useful in determining the return of menstrual function. In underweight and hypoestrogenemic adolescents with AN, the ovaries are small and amorphous, and the uterus regressed to a prepubertal size with a very thin or undetectable endometrium. As adolescents with AN gain weight, the ovaries develop small multifollicular cysts and the uterus increases in size.[47] Return to normal menstrual function correlates with the appearance of a dominant ovarian follicle and ovarian and uterine maturity. In one study, the dominant ovarian follicle correlated with premorbid weight, not simply BMI.[48] In another study, ovarian and uterine maturity was associated with return of menses within 12 months in 50% of adolescents with AN who reached 96.5% of their IBW.[49] Key *et al.*[50] showed that 88% of adolescents with AN required a weight-to-height ratio of 100% (BMI = 20), as determined by Tanner–Whitehouse British Standards, to achieve reproductive maturity on pelvic ultrasound. In this study, only 11% of patients attained ovarian and uterine maturity at 90% IBW. The authors suggest that aiming for weight gain to 90% of IBW in adolescents with AN will result in a significant percent who will remain amenorrheic or not achieve full reproductive maturity. Therefore, persistent amenorrhea may reflect the fact that an adolescent with AN is not truly "weight recovered" despite being at a weight within the normal range for their age and height.

Menstrual Function and Fat Mass

In an early study examining amenorrhea in adolescent females with AN, Frisch and McArthur[51] proposed the critical weight or fat mass hypothesis for the onset of menarche or resumption of menses. The

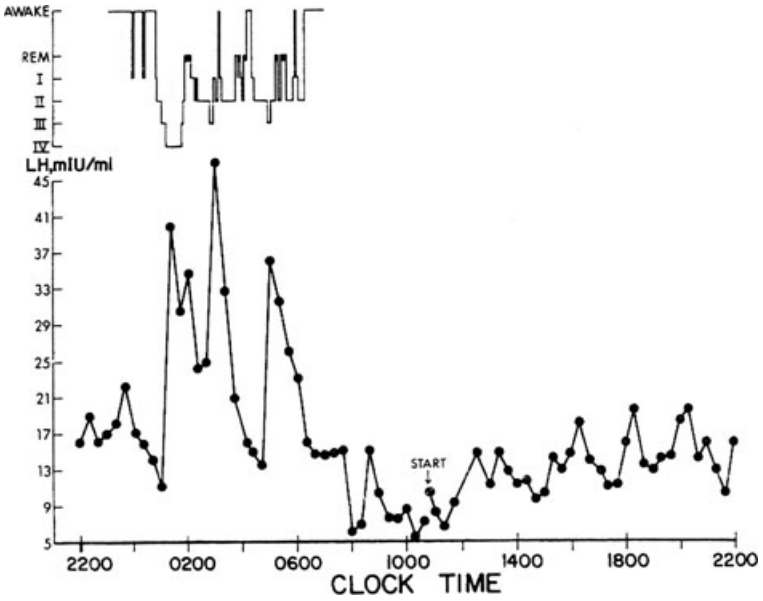

FIGURE 2. Immature 24-hour LH secretion pattern in a 20-year-old female with AN and primary amenorrhea. The pattern is characteristic of premenarche, suggesting an arrest in menstrual functioning. (From Ref. 43. Copyright © 1974 Massachusetts Medical Society. All rights reserved.)

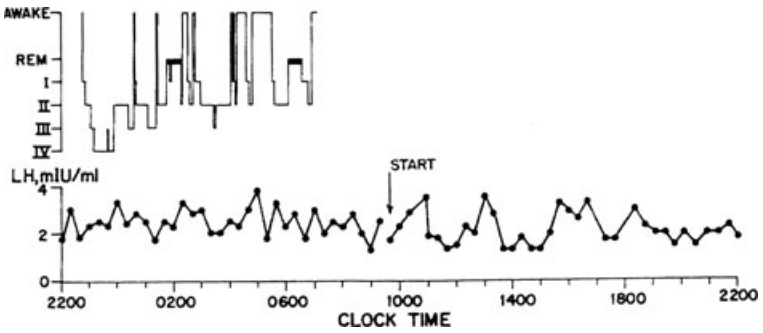

FIGURE 3. Immature 24-hour LH secretion pattern in a 21-year-old female with AN and secondary amenorrhea. The pattern shows regression to a prepubertal pattern, with low levels of LH and no pulsatility. (From Ref. 43. Copyright © 1974 Massachusetts Medical Society. All rights reserved.)

authors suggested that the minimum or threshold weight for height for menarche is at approximately 17% fat as a percentage of body weight. Additionally, the authors reported that an average of 26–28% fat as a percentage of body weight is achieved at the completion of normal growth and that a minimum weight representing 22% body fat is required for the maintenance or resumption of menses in females greater than 16 years of age.

More recently, Misra *et al.*[52] demonstrated that high baseline cortisol levels predict increases in body fat and that increases in body fat predicted recovery of menses in adolescents with AN. When menses-recovered young women with AN were compared both with those who had not recovered their menses and with controls, menses-recovered women had higher baseline cortisol levels and greater increases in leptin than did controls and greater increases in fat mass than women not menses-recovered and controls. In a logistic regression model, increasing fat mass predicted menstrual recovery and baseline cortisol levels strongly predicted increases in the percentage of body fat.[52]

The reasons for preservation of menstrual function in some very underweight patients are unclear. Miller *et al.*[53] studied 116 underweight young adult women in their 20s. Seventy-four of the subjects met all the criteria for AN, while the remaining 42 subjects met all criteria for AN except for amenorrhea. The two

groups did not differ in percent IBW (determined by the 1959 Metropolitan Life Tables), BMI, duration of AN, age at menarche, and hours per week of exercise. However, the menstruating group had a significantly different body composition with a higher fat mass, visceral fat mass, and percent body fat. This study suggested that relative sparing of fat mass in the face of severe malnourishment may be critical to the preservation of menstrual function. In addition, menstruating patients were also found to have higher levels of leptin and insulin-like growth factor I (IGF-I), which are discussed in greater detail in the next section.

Menstrual Function and Leptin

Low levels of the hormone leptin may contribute to the hypogonadism of starvation. Leptin is a protein hormone secreted by adipocytes that is involved in energy homeostasis. Leptin levels are thought to represent the fat stores in the body[54]and are a major trigger hormone for the adaptation to starvation.[55] Leptin levels have been found to be lower in patients with AN compared with controls.[56] Leptin has also been shown to predict fat mass and eating-disordered behavior in both malnourished patients with AN as well as during the process of recovery.[57–59] Additionally, there is increasing evidence that leptin plays a critical role in reproduction. Hypoleptinemia is associated with reduced levels of LH and estradiol and may also act directly at the level of the pituitary gland and ovary where leptin receptors are present.[60] A leptin level less than 2 μg/L has been proposed as the critical threshold value for amenorrhea.[60,61] In a comparison of 43 underweight females and 63 females with either AN or BN, only leptin predicted a lifetime occurrence of amenorrhea, whereas BMI, fat mass, and percent body fat did not predict the lifetime occurrence of amenorrhea.[61] Fasting leads to decreased leptin levels before the onset of weight loss and may explain why, in some patients, amenorrhea occurs before the onset of weight loss.

Exogenous administration of recombinant human leptin has been shown to improve reproductive function in women with hypothalamic amenorrhea. Welt *et al.*[62] administered twice-daily recombinant human leptin over 3 months to eight women with hypothalamic amenorrhea due to strenuous exercise or low weight (within 15% IBW) who did not have active eating disorders. These subjects were compared to six controls with hypothalamic amenorrhea who did not receive recombinant human leptin. Treatment with recombinant human leptin increased mean LH levels and LH pulse frequency and increased maximal follicular diameter, the number of dominant follicles, ovarian volume and estradiol levels. Three of these patients achieved an ovulatory menstrual cycle, which was higher than the expected rate of spontaneous ovulation of 10 percent.

Like other factors, the return of normal leptin levels is not in and of itself sufficient for the return of normal menstrual function. Leptin, like most neuroendocrine hormones, works in concert with other factors contributing to the menstrual dysfunction observed in patients with AN. This is underscored by work that has shown that both eumenorrheic and amenorrheic weight-recovered patients with AN have both similar and normal leptin levels; however, those with amenorrhea have low estradiol and growth hormone (GH) levels.[63] Since low levels of leptin are correlated with low levels of IGF-I in women with AN, it may be that collectively nutritional status, levels of IGF-I, and levels of leptin contribute to menstrual dysfunction in AN. The exact role of leptin action in the pathophysiology of the menstrual function and AN needs to be further elucidated.

Menstrual Function and Disordered Eating

In as many as two-thirds of patients with AN, absence of menses precedes significant weight loss.[64,65] This suggests that factors other than significant weight loss contribute to the amenorrhea of AN. For instance, in many young women with AN, disordered eating behaviors, particularly caloric restriction, precede the attainment of low weight. The effect of disordered eating on the menstrual cycle has been investigated. Two groups investigated the effect of caloric restriction on LH and GnRH in the menstrual cycle in women who did not have an eating disorder.[66,67] Loucks *et al.*[66] used hormone assay analyses to examine the effects of exercise and disordered eating on serum hormone levels. Their results indicate that low serum LH in exercising women is caused by low energy availability rather than by exercise. Similarly, Warren and Perlroth[67] reported that the primary cause of GnRH suppression in athletes is caloric restriction.

These conclusions are further supported by work done in woman with functional hypothalamic amenorrhea (FHA). Marcus *et al.*[68] conducted a study to determine whether disordered eating distinguished women with FHA from those with organic causes of amenorrhea and eumenorrheic controls. Women with FHA reported significantly more symptoms of disordered eating than did either eumenorrheic women or women with organic amenorrhea. Schneider *et al.*[69] also looked at FHA and its relationship with grehlin, a hormone secreted by the stomach in response to hunger, and disordered eating. They found that both ghrelin and

eating behaviors (as measured by the Eating Attitudes Test) were significantly elevated in FHA, even in light of normal caloric intake. They proposed that ghrelin acts as a restraining metabolic signal preventing the return of regular menses in women with both disordered eating and FHA.

Menstrual Function and Exercise

Excessive exercise is commonly seen in patients with AN.[70,71] Excessive exercise in non–eating-disordered athletes has been associated with menstrual irregularities. Exercise-induced amenorrhea has an incidence of 5 to 25%, depending on the type and level of activity, and is due to hypothalamic dysfunction associated with a decrease in pulse frequency of GnRH, with ensuing low levels of LH, FSH, and estradiol.[72] When combined with malnutrition and weight loss, exercise increases the likelihood of amenorrhea developing sooner and for a longer time. Litt and Glader[73] compared exercising and sedentary females with AN and found that exercisers with AN had a greater degree of menstrual dysfunction and took longer to resume menses following weight gain.

The female athlete triad is defined as the combination of disordered eating, amenorrhea, and osteoporosis. This is reviewed in greater detail in the chapter by Golden and Carlson in this volume. The female athlete triad is caused by an imbalance between energy intake and energy expenditure.[66,67] This in turn stimulates compensatory mechanisms, such as weight loss or energy conservation, subsequently causing a central suppression of reproductive function and concomitant hypoestrogenism.

Menstrual Function and Psychological Stressors

As mentioned previously, menstrual dysfunction in adolescents with eating disorders is a complex phenomenon. Persistent amenorrhea may reflect the fact that young people with AN are not actually "weight recovered" or that weight may not be the sole factor contributing to the amenorrhea. For instance, psychological recovery has been shown to be an important feature contributing to resumption of menses in AN. One study followed a cohort of women for one year post treatment for AN.[74] Those patients who were weight-recovered but amenorrheic tended to have eating attitudes and behaviors consistent with AN. For example, these young women restricted their fat intake, were preoccupied with food and a thin ideal body, had fears of becoming fat, and had a distorted body image to a greater extent than those with return of menses. In addition, affective and/or anxiety disorders occur in 33–73% of young women with AN.[25,75–77] Major depression, anxiety, and stress are associated with increased cortisol secretion and resistance to the negative feedback of cortisol on cortisol-releasing hormone (CRH), resulting in inhibition of GnRH secretion.[78] When depression, anxiety, or stress occur concurrently with an eating disorder, the effect of weight loss on the hypothalamic-pituitary-gonadal (HPG) axis may be compounded and contribute to amenorrhea.[78]

Bulimia Nervosa

Women with BN can experience abnormalities in menstrual function. Unfortunately, the effect of BN on menstrual function is not well studied in adolescents.[79] Menstrual dysfunction and oligomenorrhea occur in approximately half of women with BN (range 37–64%), while amenorrhea occurs in 5–40%.[6,31–37] In women with BN who have a prior history of AN, the prevalence of secondary amenorrhea is as high as 77%.[6] Menstrual dysfunction in women with BN has been associated with lifetime minimum BMI, a history of weight loss or AN, low caloric and dietary fat intake, high frequency of vomiting, binge eating, use of appetite suppressants, exercise frequency, and low thyroxin concentrations.[6,36,80] Perpetuation of menstrual dysfunction in women treated for BN has been associated with fluctuations in body weight, depression, and cigarette smoking, suggesting that these may act as ongoing metabolic stressors leading to menstrual dysfunction.[36]

Menstrual dysfunction in BN is associated with disruption of the HPG axis. Some normal-weight women with BN have low LH and FSH levels, low estradiol, and reduced 24-hour LH secretion patterns.[34,80–85]

There is also an association between BN and polycystic ovary syndrome (PCOS) which may contribute to the menstrual dysfunction observed in woman with BN. The prevalence of PCOS in BN has been reported to be as high as 76–100% when only ovarian morphology is examined using ultrasound.[86–88] However, the prevalence of PCOS was 16.6% among young adult women with BN compared to 5–10% in the general population when clinical features, biochemical markers and ovarian morphology were all used to establish a diagnosis of PCOS.[85] Finally, patients with PCOS have been shown to have a high prevalence of BN.[89,90] The mechanism(s) for the association between BN and PCOS is unknown. Naessen *et al.*[85] have proposed that PCOS in the context of BN may be secondary to (1) disordered eating behaviors, such as binge eating, which may lead to abnormal insulin-induced increases in androgen concentrations or (2) that the hyperandrogenism of PCOS predisposes to the development

of bulimic behavior by stimulating appetite, impairing impulse control, or causing irritability and depression.

Complications of Menstrual Dysfunction

Menstrual dysfunction in adolescents with eating disorders can have far-reaching effects and exert a significant impact on growth and pubertal development, peak bone mass acquisition, and cognitive function. These complications may not be completely reversible.

Growth and Pubertal Development

Eating disorders often present with the onset of puberty, when normal changes in body composition may combine with the developmental challenges of adolescence to produce body image disturbance. The resulting malnutrition may result in pubertal delay or arrest.[91,92] Pubertal delay is a common finding in adolescents who develop AN prior to the completion of puberty. Seventeen percent of adolescents with AN of the restricting type have sexual maturity ratings that were 2 standard deviations below the mean for age.[91] Of particular concern is the effect that eating disorders can have on achievement of normal menarche. Misra *et al.*[93] found that of the female adolescents who had AN and had not attained menarche, 94% were above the mean age at menarche (12.8 years) for white girls in the United States and 35% were delayed more than 2 standard deviations (>15.3 years). In those who had attained menarche, 32% had menarche at an age greater than the mean age of menarche.[93] Others have also found the age of menarche to be delayed in females with early-onset AN compared to healthy adolescent females.[92]

Impairment of linear growth and permanent short stature occur in some adolescents with eating disorders.[5] During normal puberty, estrogen levels increase simultaneously with increases in GH and IGF-I. Both estrogen and IGF-I are bone-trophic hormones that stimulate longitudinal bone growth. Regulation of longitudinal bone growth is likely due to a complex interplay between estrogen, other hormones, and the GH-IGF axis.[94] Levels of estrogen and IGF-I are low in adolescents with AN, which may contribute to alterations in linear growth.[93,95]

Peak Bone Mass

Peak bone mass acquisition occurs during adolescence.[5] The development of an eating disorder during adolescence can result in failure to acquire peak bone mass and result in low bone mineral density with a potential increased risk for fractures.[96] Failure to acquire peak bone mass is related to the menstrual disturbances that occur in eating disorders and is discussed in more detail in the chapter by Dr. Misra in this volume.

Cognitive Function

Brain development involves increases in total white and occipital gray-matter volumes from ages 4 to 20 years in healthy children and adolescents, while temporal gray-matter volumes increases in childhood and adolescence, reaching a maximum at age 16.7 years and then declines.[97,98] Research on brain changes in AN suggests that the development of an eating disorder during this critical developmental period may cause structural and functional changes that may or may not be reversible.[99–104] MRI studies[99]have demonstrated increased cerebrospinal fluid (CSF) volumes associated with decreased total gray- and total white-matter volumes in adolescent females with AN compared to healthy controls. In a cross-sectional and longitudinal follow-up study,[105] patients who had recovered from AN showed persistent increases in CSF volume and deficits in gray matter compared to healthy controls; however, these values were both improved when compared to values in low-weight patients with AN. In a long-term follow-up study of brain structure and cognitive function, women with adolescent-onset AN had larger lateral and third ventricles and showed cognitive deficits over a broad range of neuropsychological domains. Both weight recovery and cortisol were important modifiers of the structural brain changes. However, the women that remained amenorrheic had deficits in cognitive function across a variety of domains, including recall, verbal memory, working memory, visual reproduction, reading, math, and oral language.[106] Low circulating levels of estrogen have been shown to have an adverse impact on cognition in postmenopausal women, surgically menopausal women, and women with premature ovarian failure and Turner syndrome.[107–109] The relationship between amenorrhea and cognition in AN has yet to be fully elucidated.

Conclusions

Menstrual dysfunction is a common feature of all types of eating disorders.[6] The etiology of menstrual dysfunction in adolescents with eating disorders is multifaceted and the result of a complex interplay of many factors including body weight, body fat, leptin and other hormones, eating attitudes and behaviors, exercise, and psychological stressors. This is further complicated by the fact that eating disorders are common

among adolescent girls, a time of profound physical and mental growth and development. The significance of menstrual dysfunction in adolescents with eating disorders is particularly important when considering its impact on linear growth, pubertal development, bone mineral accretion, and cognitive functioning.

Research on menstrual dysfunction in eating disorders has produced a base of knowledge, albeit one with major gaps. Most of the research on menstrual function and eating disorders has focused on adults, and the findings may not apply to younger individuals. Thus, the research agenda for menstrual function and eating disorders among adolescents is vast.

Further study of the many factors that influence menarche and menstruation is needed. The identification of clinically useful biological markers to predict menarche and return of menstrual function is critical in the treatment and prevention of significant morbidity in this population. Menstrual dysfunction in adolescents with eating disorders has far reaching effects. Future research in patients with AN will help us appreciate the impact of estrogen on cognition and this may have important implications for understanding the treatment and prognosis of AN. Finally, research on the causes of menstrual dysfunction in adolescents with eating disorders will provide researchers and clinicians with a clearer understanding of the physical and psychological implications that these disorders can have on the adolescent's overall health.

Conflicts of Interest

Dr. Katzman received NIH funding.

References

1. Fisher, M., N.H. Golden & D.K. Katzman, *et al*. 1995. Eating disorders in adolescents: a background paper. J. Adolesc. Health **16:** 420–437.
2. Sullivan, P. 1995. Mortality in anorexia nervosa. Am. J. Psychiatry **152:** 1073–1074.
3. Steiner, H. & J. Lock. 1998. Anorexia nervosa and bulimia nervosa in children and adolescents: a review of the past 10 years. J. Am. Acad. Child Adolesc. Psychiatry **37:** 352–359.
4. Rome, E.S. & S. Ammerman. 2003. Medical complications of eating disorders: an update. J. Adolesc. Health **33:**418–426.
5. Katzman, D.K. 2005. Medical complications in adolescents with anorexia nervosa: a review of the literature. Int. J. Eat. Disord. **37:** S52–S59.
6. Pinheiro, A.P., L.M. Thornton & K.H. Plotonicov, *et al*. 2007. Patterns of menstrual disturbance in eating disorders. Int. J. Eat. Disord. **40:** 424–434.
7. American Psychiatric Association. 2000. Diagnostic and Statistical Manual of Mental Disorders, 4th ed., text revision (DSM-IV-TR). American Psychiatric Association. Washington, DC.
8. Nicholls, D., R. Chater & B. Lask. 2000. Children into DSM don't go: a comparison of classification systems for eating disorders in childhood and early adolescence. Int. J. Eat. Disord. **28:** 317–324.
9. Golden, N.H., D.K. Katzman & R.E. Kreipe, *et al*. 2003. Eating disorders in adolescents. J. Adolesc. Health **33:** 496–503.
10. Workgroup for Classification of Eating Disorders in Children and Adolescents. 2007. Classification of child and adolescent eating disturbances. Int. J. Eat. Disord. **40:** S117–S122.
11. Hoek, H.W. & D. van Hoeken. 2003. Review of the prevalence and incidence of eating disorders. Int. J. Eat. Disord. **34:** 383–396.
12. Bulik, C.M., P.F. Sullivan, F. Tozzi, *et al*. 2006. Prevalence, heritability, and prospective risk factors for anorexia nervosa. Arch. Gen. Psychiatry **63:** 305–312.
13. Herzog, D.B., M.B. Keller & P.W. Lavori. 1988. Outcome in anorexia nervosa and bulimia nervosa: a review of the literature. J. Nerv. Ment. Dis. **176:** 131–143.
14. Ratnasuriya, R., I. Eisler, G. Szmukler & G. Russell. 1991. Anorexia nervosa: outcome and prognostic factors after 20 years. Br. J. Psychiatry **158:** 495–502.
15. Steinhausen, H., Christoph & R. Seidel. 1993. Outcome in adolescent eating disorders. Int. J. Eat. Disord. **14:** 487–496.
16. Casper, R.C. & L.N. Jabine. 1996. An eight-year follow-up: Outcome from adolescent compared to adult onset anorexia nervosa. J. Youth Adolesc. **25:** 499–517.
17. Herpertz-Dahlmann, B.M., C. Wewetzer, E. Schulz & H. Remschmidt. 1996. Course and outcome in adolescent anorexia nervosa. Int. J. Eat. Disord. **19:** 335–345.
18. Herpertz-Dahlmann, B.M., C. Wewetzer, E. Schulz & H. Remschmidt. 1996. Outcome, psychosocial functioning, and prognostic factors in adolescent anorexia nervosa as determined by prospective follow-up assessment. J. Youth Adolesc. **25:** 455–471.
19. Wentz, E., C. Gillberg, I.C. Gillberg & M. Rastam. 2001. Ten-year follow-up of adolescent-onset anorexia nervosa: psychiatric disorders and overall functioning scales. J. Child. Psychol. Psychiat. **42:** 613–622.
20. Fichter, M.M. & N. Quadflieg. 1997. Six-year course of bulimia nervosa. Int. J. Eat. Disord. **22:** 361–384.
21. Keel, P.K., J.E. Mitchell, K.B. Miller, T.L. Davis & S.J. Crow. 1999. Long-term outcome of bulimia nervosa. Arch. Gen. Psychiatry **56:** 63–69.
22. Herzog, D.B., D.J. Dorer & P.K. Keel, *et al*. 1999. Recovery and relapse in anorexia and bulimia nervosa: a 7.5-year follow-up study. J. Am. Acad. Child Adolesc. Psychiatry **38:** 829–837.
23. Fairburn, C.G., P.A. Norman, S.L. Welch, *et al*. 1995. A prospective study of outcome in bulimia nervosa and the long-term effects of three psychological treatments. Arch. Gen. Psychiatry **52:** 304–312.
24. Fairburn, C.G., Z. Cooper, H.A. Doll, *et al*. 2000. The natural course of bulimia nervosa and binge eating disorder in young women. Arch. Gen. Psychiatry **57:** 659–665.

25. Laessle, R.G., H.U. Wittchen, M.M. Fichter & K.M. Pirke. 1989. The significance of subgroups of bulimia and anorexia nervosa: lifetime frequency of psychiatric disorders. Int. J. Eat Disord. **8:** 569–574.
26. Turner, H. & R. Bryant-Waugh. 2004. Eating disorder not otherwise specified (EDNOS): profiles of clients presenting at a community eating disorder service. Eur. Eat. Disord. Rev. **12:** 18–26.
27. Fairburn, C.G. & K. Bohn. 2005. Eating disorder NOS (EDNOS): an example of the troublesome "not otherwise specified" (NOS) category in DSM-IV. Behav. Res. Ther. **43:** 691–701.
28. Fairburn, C.G., Z. Cooper, K. Bohn, *et al*. 2007. The severity and status of eating disorder NOS: Implications for DSM-V. Behav. Res. Ther. **45:** 1705–1715.
29. Peebles, R., J.L. Wilson & J.D. Lock. 2006. How do children with eating disorders differ from adolescents with eating disorders at initial evaluation? J. Adolesc. Health **39:** 800–805.
30. Ricca, V., E. Mannucci & B. Mezzani, *et al*. 2001. Psychopathological and clinical features of outpatients with an eating disorder not otherwise specified. Eating Weight Disord. **6:** 157–165.
31. Fairburn, C.G. & P.J. Cooper. 1982. Self-induced vomiting and bulimia nervosa: an undetected problem. Br. Med. J. (Clinical Research edition) **284:** 1153–1155.
32. Fairburn, C. & P. Cooper. 1984. The clinical features of bulimia nervosa. Br. J. Psychiatry **144:** 238–246.
33. Garner, D., P. Garfinkel & M. O'Shaughnessy. 1985. The validity of the distinction between bulimia with and without anorexia nervosa. Am. J. Psychiatry **142:** 581–587.
34. Pirke, K.M., M.M. Fichter & C. Chlond, *et al*. 1987. Disturbances of the menstrual cycle in bulimia nervosa. Clin. Endocrinol. **27:** 245–251.
35. Cantopher, T., C. Evans, J.H. Lacey & J.M. Pearce. 1988. Menstrual and ovulatory disturbance in bulimia. Br. Med. J. **297:** 836–837.
36. Gendall, K.A., C.M. Bulik, P.R. Joyce, *et al*. 2000. Menstrual cycle irregularity in bulimia nervosa. J. Psychosom. Res. **49:** 409–415.
37. Crow, S.J., P. Thuras, P.K. Keel & J.E. Mitchell. 2002. Long-term menstrual and reproductive function in patients with bulimia nervosa. Am. J. Psychiatry **159:** 1048–1050.
38. Garfinkel, P., E. Lin & P. Goering, *et al*. 1996. Should amenorrhoea be necessary for the diagnosis of anorexia nervosa? Evidence from a Canadian community sample. Br. J. Psychiatry **168:** 500–506.
39. Marshall, J.C. & T.R. Fraser. 1971. Amenorrhea in anorexia nervosa: assessment and treatment with clomiphene citrate. Br. Med. J. **4:** 590–592.
40. Marshall, J. & R. Kelch. 1979. Low dose pulsatile gonadotropin-releasing hormone in anorexia nervosa: a model of human pubertal development. J. Clin. Endocrinol. Metab. **49:** 712–718.
41. Sherman, B., K. Halmi & R. Zamudio. 1975. LH and FSH response to gonadotropin-releasing hormone in anorexia nervosa: effect of nutritional rehabilitation. J. Clin. Endocrinol. Metab. **41:** 135–142.
42. Kakarla, N. & K.D. Bradshaw. 2003. Disorders of pubertal development: precocious puberty. Semin. Reprod. Med. **21:** 339–351.
43. Boyar, R.M., J. Katz & J.W. Finkelstein, *et al*. 1974. Anorexia nervosa: immaturity of the 24-hour luteinizing hormone secretory pattern. N. Engl. J. Med. **291:** 861–865.
44. Golden, N.H., M.S. Jacobson, J. Schebendach, *et al*. 1997. Resumption of menses in anorexia nervosa. Arch. Pediatr. Adolesc. Med. **151:** 16–21.
45. Shomento, S.H. & R.E. Kreipe. 1994. Menstruation and fertility following anorexia nervosa. Adolesc. Pediatr. Gynecol. **7:** 142–146.
46. Swenne, I. 2004. Weight requirements for return of menstruations in teenage girls with eating disorders, weight loss and secondary amenorrhoea. Acta Paediat. **93:** 1449–1455.
47. Mason, H.D., A. Key, R. Allan & B. Lask. 2007. Pelvic ultrasonography in anorexia nervosa: what the clinician should ask the radiologist and how to use the information provided. Eur. Eat. Disord. Rev. **15:** 35–41.
48. Treasure, J.L. 1988. The ultrasonographic features in anorexia nervosa and bulimia nervosa: a simplified method of monitoring hormonal states during weight gain. J. Psychosom. Res. **32:** 623–634.
49. Lai, K., R. Bruyn, B. Lask, *et al*. 1994. Use of pelvic ultrasound to monitor ovarian and uterine maturity in childhood onset anorexia nervosa. Arch. Dis. Child. **71:** 228–231.
50. Key, A., H. Mason, R. Allan & B. Lask. 2002. Restoration of ovarian and uterine maturity in adolescents with anorexia nervosa. Int. J. Eat. Disord. **32:** 319–325.
51. Frisch, R.E. & J.W. McArthur. 1974. Menstrual cycles: fatness as a determinant of minimum weight for height necessary for their maintenance or onset. Science **185:** 949–951.
52. Misra, M., R. Prabhakaran & K.K. Miller, *et al*. 2006. Role of cortisol in menstrual recovery in adolescent girls with anorexia nervosa. Pediatr. Res. **59:** 598–603.
53. Miller, K.K., S. Grinspoon & S. Gleysteen, *et al*. 2004. Preservation of neuroendocrine control of reproductive function despite severe undernutrition. J. Clin. Endocrinol. Metab. **89:** 4434–4438.
54. Matejek, N., E. Weimann, C. Witzel, *et al*. 1999. Hypoleptinaemia in patients with anorexia nervosa and in elite gymnasts with anorexia athletica. Int. J. Sports Med. **20:** 451–456.
55. Chan, J.L. & C.S. Mantzoros. 2005. Role of leptin in energy-deprivation states: normal human physiology and clinical implications for hypothalamic amenorrhoea and anorexia nervosa. Lancet **366:** 74–85.
56. Mehler, P.S., R.H. Eckel & W.T. Donahoo. 1999. Leptin levels in restricting and purging anorectics. Int. J. Eat. Disord. **26:** 189–194.
57. Nakai, Y., S. Hamagaki, S. Kato, *et al*. 1999. Role of leptin in women with eating disorders. Int. J. Eat. Disord. **26:** 29–35.
58. Nakai, Y., S. Hamagaki, S. Kato, *et al*. 1999. Leptin in women with eating disorders. Metabolism **48:** 217–220.

59. Morgan, J.F., J. Bolton, P.M. Sedgwick, *et al*. 1999. Changes in plasma concentrations of leptin and body fat composition during weight restoration in anorexia nervosa. J. Clin. Endocrinol. Metab. **84:** 2257.
60. Hebebrand, J., T.D. Muller, K. Holtkamp & B. Herpertz-Dahlmann. 2007. The role of leptin in anorexia nervosa: clinical implications. Mol. Psychiatry **12:** 23–35.
61. Kopp, W., W.F. Blum & S. von Prittwitz, *et al*. 1997. Low leptin levels predict amenorrhea in underweight and eating disordered females. Mol. Psychiatry **2:** 335–340.
62. Welt, C.K., J.L. Chan & J. Bullen, *et al*. 2004. Recombinant human leptin in women with hypothalamic amenorrhea. N. Engl. J. Med. **351:** 987–997.
63. Audi, L., C.S. Mantzoros, A. Vidal-Puig, *et al*. 1998. Leptin in relation to resumption of menses in women with anorexia nervosa. Mol. Psychiatry **3:** 544–547.
64. Halmi, K.A. 1974. Anorexia nervosa: demographic and clinical features in 94 cases. Psychosomatic Med. **36:** 18–26.
65. Hurd, H.P., P.J. Palumbo & H. Gharib. 1977. Hypothalamic-endocrine dysfunction in anorexia nervosa. Mayo Clinic Proc. **52:** 711–716.
66. Loucks A.B., M. Verdun & E.M. Heath. 1998. Low energy availability, not stress of exercise, alters LH pulsatility in exercising women. J. Appl. Physiol. **84:** 37–46.
67. Warren, M.P. & N.E. Perlroth. 2001. The effects of intense exercise on the female reproductive system. J. Endocrinol. **170:** 3–11.
68. Marcus, M.D., T.L. Loucks & S.L. Berga. 2001. Psychological correlates of functional hypothalamic amenorrhea. Fertil. Steril. **76:** 310–316.
69. Schneider, L.F. & M.P. Warren. 2006. Functional hypothalamic amenorrhea is associated with elevated ghrelin and disordered eating. Fertil. Steril. **86:** 1744–1749.
70. Davis, C., D.K. Katzman & S. Kaptein, *et al*. 1997. The prevalence of high-level exercise in the eating disorders: etiological implications. Compr. Psychiatry **38:** 321–326.
71. Shroff, H., L. Reba & L.M. Thornton, *et al*. 2006. Features associated with excessive exercise in women with eating disorders. Int. J. Eat. Disord. **39:** 454–461.
72. Warren, M.P. 1999. Health issues for women athletes: exercise-induced amenorrhea. J. Clin. Endocrinol. Metab. **84:** 1892–1896.
73. Litt, I.F. & L. Glader. 1986. Anorexia nervosa, athletics, and amenorrhea. J. Pediatr. **109:** 150–153.
74. Falk, J.R. & K.A. Halmi. 1982. Amenorrhea in anorexia nervosa: examination of the critical body weight hypothesis. Biol. Psychiatry **17:** 799–806.
75. Halmi, K.A., E. Eckert, P. Marchi, *et al*. 1991. Comorbidity of psychiatric diagnoses in anorexia nervosa. Arch. Gen. Psychiatry **48:** 712–718.
76. Herzog, D.B., M.B. Keller, N.R. Sacks, *et al*. 1992. Psychiatric comorbidity in treatment-seeking anorexics and bulimics. J. Am. Acad. Child Adolesc. Psychiatry **31:** 810–818.
77. Geist, R., R. Davis & M. Heinmaa. 1998. Binge/purge symptoms and comorbidity in adolescents with eating disorders. Can. J. Psychiatry **43:** 507–512.
78. Young, E.A. & A. Korszun. 2002. The hypothalamic-pituitary-gonadal axis in mood disorders. Endocrinol. Metab. Clin. North Am. **31:** 63–78.
79. leGrange, D., Loeb, K., S. VanOrman & C. Jellar. 2004. Bulimia nervosa in adolescents: a disorder in evolution? Arch. Pediatr. Adolesc. Med. **158:** 478–482.
80. Schweiger, U., K. Pirke, R. Laessle & M. Fichter. 1992. Gonadotropin secretion in bulimia nervosa. J. Clin. Endocrinol. Metab. **74:** 1122–1127.
81. Pirke, K.M., M.M. Fichter, U. Schweiger, *et al*. 1987. Gonadotropin secretion pattern in bulimia nervosa. Int. J. Eat. Disord. **6:** 655–661.
82. Pirke, K.M., M. Dogs, M.M. Fichter & R.J. Tuschl. 1988. Gonadotrophins, oestradiol and progesterone during the menstrual cycle in bulimia nervosa. Clin. Endocrinol. **29:** 265–270.
83. Devlin, M.J., B.T. Walsh & J.L. Katz, *et al*. 1989. Hypothalamic-pituitary-gonadal function in anorexia nervosa and bulimia. Psychiatry Res. **28:** 11–24.
84. Resch, M., G. Szendei & P. Haász. 2004. Bulimia from a gynecological view: hormonal changes. J. Obstet. Gynaecol. **24:** 907–910.
85. Naessen, S., K. Carlstrom, L. Garoff, *et al*. 2006. Polycystic ovary syndrome in bulimic women: an evaluation based on the new diagnostic criteria. Gynecol. Endocrinol. **22:** 388–394.
86. McCluskey, S.E., J.H. Lacey & J.M. Pearce. 1992. Binge-eating and polycystic ovaries. Lancet **340:** 723.
87. Raphael, F.J., D.A. Rodin, A. Peattie, *et al*. 1995. Ovarian morphology and insulin sensitivity in women with bulimia nervosa. Clin. Endocrinol. **43:** 451–455.
88. Morgan, J.F., S.E. McCluskey, J.N. Brunton & J. Hubert Lacey. 2002. Polycystic ovarian morphology and bulimia nervosa: a 9-year follow-up study. Fertil. Steril. **77:** 928–931.
89. McCluskey, S.E., C. Evans, J.H. Lacey, *et al*. 1991. Polycystic ovary syndrome and bulimia. Fertil. Steril. **55:** 287–291.
90. Jahanfar, S., J.A. Eden & T.V. Nguyent. 1995. Bulimia nervosa and polycystic ovary syndrome. Gynecol. Endocrinol. **9:** 113–117.
91. Palla, B. & I.F. Litt. 1988. Medical complications of eating disorders in adolescents. Pediatrics **81:** 613–623.
92. Lantzouni, E., G.R. Frank, N.H. Golden & R.I. Shenker. 2002. Reversibility of growth stunting in early onset anorexia nervosa: a prospective study. J. Adolesc. Health **31:** 162–165.
93. Misra, M., A. Aggarwal & K.K. Miller, *et al*. 2004. Effects of anorexia nervosa on clinical, hematologic, biochemical, and bone density parameters in community-dwelling adolescent girls. Pediatrics **114:** 1574–1583.
94. Juul, A. 2001. The effects of oestrogens on linear bone growth. Hum. Reprod. Update **7:** 303–313.
95. Misra, M., K.K. Miller & J. Bjornson, *et al*. 2003. Alterations in growth hormone secretory dynamics in adolescent girls with anorexia nervosa and effects on bone metabolism. J. Clin. Endocrinol. Metab. **88:** 5615–5623.
96. Misra, M. & A. Klibanski. 2006. Anorexia nervosa and osteoporosis. Rev. Endocr. Metab. Disord. **7:** 91–99.

97. GIEDD, J.N., J. BLUMENTHAL & N.O. JEFFRIES, *et al*. 1999. Brain development during childhood and adolescence: a longitudinal MRI study. Nat. Neurosci. **2:** 861–863.
98. GIEDD, J.N., J. BLUMENTHAL & N.O. JEFFRIES, *et al*. 1999. Development of the human corpus callosum during childhood and adolescence: a longitudinal MRI study. Prog. Neuropsychopharmacol. Biol. Psychiatry **23:** 571–588.
99. KATZMAN D.K., E.K. LAMBE, D.J. MIKULIS, *et al*. 1996. Cerebral gray matter and white matter volume deficits in adolescent girls with anorexia nervosa. J. Pediatr. **129:** 794–803.
100. GOLDEN, N.H., M. ASHTARI & M.R. KOHN, *et al*. 1996. Reversibility of cerebral ventricular enlargement in anorexia nervosa, demonstrated by quantitative magnetic resonance imaging. J. Pediatr. **128:** 296–301.
101. GORDON, I., B. LASK, R. BRYANT-WAUGH, *et al*. 1997. Childhood-onset anorexia nervosa: towards identifying a biological substrate. Int. J. Eat. Disord. **22:** 159–165.
102. LAMBE, E.K., D.K. KATZMAN, D.J. MIKULIS, *et al*. 1997. Cerebral gray matter volume deficits after weight recovery from anorexia nervosa. Arch. Gen. Psychiatry **54:** 537.
103. LASK, B., I. GORDON, D. CHRISTIE, *et al*. 2005. Functional neuroimaging in early-onset anorexia nervosa. Int. J. Eat. Disord. **37:** S49–S51.
104. FRANK, G.K., U.F. BAILER & C.C. MELTZER, *et al*. 2007. Regional cerebral blood flow after recovery from anorexia or bulimia nervosa. Int. J. Eat. Disord. **40:** 488–492.
105. KATZMAN, D.K., R.B. ZIPURSKY, E.K. LAMBE & D.J. MIKULIS. 1997. A longitudinal magnetic resonance imaging study of brain changes in adolescents with anorexia nervosa. Arch. Pediatr. Adolesc. Med. **151:** 793–797.
106. CHUI, H.T., B. CHRISTENSEN, R.B. ZIPURSKY & D.K. KATZMAN. 2007. Effects of menstrual function and weight restoration on cognitive function in females with adolescent-onset anorexia nervosa. J. Adolesc. Health **40:** S12–S12.
107. MILLER, K.J., J.C. CONNEY, N.L. RASGON, *et al*. 2002. Mood symptoms and cognitive performance in women estrogen users and nonusers and men. J. Am. Geriatr. Soc. **50:** 1826–1830.
108. NAPPI, R.E., E. SINFORIANI, M. MAURI, *et al*. 1999. Memory functioning at menopause: impact of age in ovariectomized women. Gynecol. Obstet. Invest. **47:** 29–36.
109. ROSS, J.L., G.A. STEFANATOS & H. KUSHNER, *et al*. 2004. The effect of genetic differences and ovarian failure: Intact cognitive function in adult women with premature ovarian failure versus Turner syndrome. J. Clin. Endocrinol. Metab. **89:** 1817–1822.