

Menstrual Dysfunction and Eating Disorders: An Overview of the Mechanisms Involved in the Pathogenesis

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ABSTRACT

Menstrual dysfunction is a common correlate across women with Eating Disorders. The onset of Eating Disorders commonly occurs during adolescence and it can lead to severe medical complications, such as pubertal delay, deficits in peak bone mass acquisition, altered physical and cognitive development. The pathogenesis of menstrual dysfunction in Eating Disorders is complicated and involves several factors such as hypothalamic-pituitary-ovarian axis impairment, low body fat, hypoleptinemia, increase of androgen levels, abnormal eating behaviors, physical exercise and psychological stressors. This chapter aims to provide a clinical overview of the several pathogenetic mechanisms underlying menstrual dysfunction.

Keywords: Eating disorders; Menstrual dysfunction; Amenorrhea

Abbreviations: ED: Eating Disorders; AN: Anorexia Nervosa; BN: Bulimia Nervosa; BED: Binge Eating Disorders

INTRODUCTION

Eating Disorders (ED) are characterized by high rates of relapse and a chronic course which may lead to severe consequences for women's well-being [1].

Most of the ED falls into one of following three categories: Anorexia Nervosa (AN), Bulimia Nervosa (BN), Binge Eating Disorder (BED). AN is characterized by restriction of energy intake leading to a significantly low body weight, fear of fatness, body weight and shape disturbances; BN is defined by recurrent episodes of binge eating followed by compensatory behaviors such as self-induced vomiting, misuse of laxatives, diuretics, fasting or over-exercise in order to prevent gain weight. Finally, individuals with BED usually are engaged in binge eating without compensatory behaviors [2].

Menstrual dysfunction occurs in all types of ED psychopathology. The mechanisms underlying menstrual dysfunction are complicated and involve several factors such as weight loss, physical exercise, hormones, low body fat, hypoleptinemia, increase of androgen levels, abnormal eating behaviors, and psychological stressors. These mechanisms will be examined more in detail below.

MENSTRUAL DYSFUNCTION AND ANOREXIA NERVOSA (AN)

Amenorrhea is the most frequent menstrual dysfunction occurring in AN and one of its necessary diagnostic criteria in DSM IV.

Amenorrhea is defined as the absence of menstrual periods in a woman of reproductive age. Primary amenorrhea is diagnosed when menarche does not occur or it does so after 16 years of age [3,4]. According to DSM IV, secondary amenorrhea is defined as "the absence of at least three consecutive menstrual cycles". In addition, DSM-IV specifies that "a woman is considered to have amenorrhea if her periods occur only following hormone-replacement therapy, e.g., estrogen administration" [5].

The clinical usefulness of this criterion has been questioned for many years [6,7]. The first concern was that a diagnosis of Eating Disorder Not Otherwise Specified (EDNOS) in patients who met all of the AN criteria but amenorrhea could give to patients the false impression of not having a problem of clinical severity. Other concerns raised related to: (i) the difficulties in diagnosing women taking anticonceptual therapies, (ii) the non-applicability to males and (iii) the lack of treatment reimbursement from insurance companies or National Health Care System for an EDNOS diagnosis [8].

Although amenorrhea is no longer a necessary diagnostic criterion for the definition of AN in DSM-5, it is beyond doubt that menstrual dysfunction is frequently observed in patients with ED.

Menstrual dysfunction pathophysiology is commonly believed to be due to weight loss leading to hypothalamic impairment, particularly to Luteinizing Hormone (LH) secretory patterns [9]. Women with AN have decreased Gonadotropin-Releasing Hormone (GnRH) secreted by the

hypothalamus, low serum concentrations of Luteinizing Hormone (LH), Follicular- Stimulating Hormone (FSH), and estradiol. LH secretion patterns increase from childhood to adulthood: while in the pre-pubertal period LH secretion is constantly low during day and night, as puberty advances LH secretion increases, occurring both day and night and remaining high during night. By adulthood, LH secretion becomes episodic arising during waking and sleeping [2]. In an early study, Boyar et al. analyzed 24 hours-LH secretion in nine women with AN aged between 17 and 23 years old. They found that eight out of nine women presented age-inappropriate patterns similar to those of pre-pubertal or pubertal children. This suggests that AN causes substantial impairment resulting in a regression (in patients with secondary amenorrhea) or an arrest (in those with primary amenorrhea) of Hypothalamic-Pituitary-Ovarian axis [10].

Frisch et al. investigated the percentage of fat mass necessary for the onset and resumption of menses. They found that a minimum of 17% of fat out of the total body weight is required to have menses that 26-28% is the percentage of fat achieved at the end of the normal growth and 22% of body fat is required in order to maintain or resume menses [11].

These results were confirmed years later in a study aimed at understanding why some women who met criteria for AN amenorrhea maintained their menses despite their low weight. They found that patients with eumenorrhea had higher fat mass percentage and higher leptin levels compared to the amenorrhoeic counterparts with similar weight [12]. Therefore fat mass and consequently leptin secretion seem to be important for the maintenance of menstruation in severely emaciated women.

A study comparing menses-recovered patients, patients who had not recovered their periods, and healthy controls found that menses-recovered AN individuals had higher baseline cortisol levels and significantly higher increases in fat mass than amenorrhoeic patients and controls. Moreover, high baseline cortisol level strongly predicted an increase in body fat percentage and that increase in body fat predicted menses recovery in patients with AN [13].

Furthermore, depression and anxiety symptoms often comorbid with AN [14], may also be responsible for increasing cortisol levels, condition that can lead to an inhibition of cortisol-releasing hormone with a subsequent inhibition of GNRH secretion [15]. When depression and anxiety are concurrent with weight loss, they can have an additive impact on hypothalamic-pituitary-gonadal axis contributing to amenorrhea.

Leptin is a hormone secreted by adipocytes implicated in the pathogenesis of amenorrhea. Compared to healthy controls, AN have been found to have lower leptin levels, possibly due to their lower fat mass [16]. In a study looking at the role of leptin on ED psychopathology and reproductive functions, the authors found a statistically significant association between leptin levels, body fat mass, eating behavior score and menstrual status score. These findings suggest that leptin levels may have a role in counteracting the effects of bingeing behaviors and in reproductive functions and they seem to predict fat mass in patients with ED [17]. Since leptin

modulates LH and estradiol secretion and it is particularly implicated in regulating LH nocturnal secretion during mid-late follicular phase, reduced leptin secretion leads to impairments in hypothalamic-pituitary-ovarian function [18].

Patients with AN and underweight healthy individuals have leptin levels respectively below and above 2 µg/l suggesting this to be a critical threshold for the maintenance of menses [19]. An increase of leptin levels and consequently of the gonadotropin are not enough to rapidly resume menstruation and evidence exists suggesting a more complex pathophysiology. In fact it has been reported that in two-third of patients with AN amenorrhea precedes weight loss and endures in recovered patients [20]. Compared to remenorrhic patients, weight-recovered amenorrhic patients report low LH concentrations and reduced LH pulse frequency, absence of a mature secretory pattern and lower plasma estradiol levels [21,22]. Nevertheless, to date the reasons why some weight-recovered patients are still amenorrhic and have such endocrinological alteration, while others normally resume regular periods and normal endocrine functions are unexplained. Some studies hypothesize a role of psychopathological factors in the maintenance of amenorrhea in weight-recovered patients. The presence of anorexia-related symptoms in these individuals including body shape and inner stimuli disturbances, impaired sense of well-being and compromised sexual behaviors [22] but also fear of fatness, drive for thinness, body dissatisfaction, ineffectiveness and interpersonal distrust [21] could affect patterns of menstruation. The persistence of some psychopathological aspects and subsequent eating attitudes and behaviors, consistent with AN in weight-recovered patients might predict relapses and suggest that factors other than malnutrition are involved in the maintenance of amenorrhea.

Excessive physical exercise is frequently observed in individuals with AN [23]. It is demonstrated that over-exercising is also associated with menstrual dysfunction in healthy athletes. The hypothesised pathophysiological mechanism is a hypothalamic dysfunction leading to a decreased pulse frequency of GnRH and consequently to reduced LH, Follicle-Stimulating Hormone (FSH) and estradiol secretion [24]. Lower gonadotropin levels, longer period of amenorrhea and a longer period to have their normal menses resumed have been documented in exercising anorectic patients compared to inactive ones [25] suggesting that over-exercising increases the likelihood of amenorrhea development in an already undernourished individual.

A recent study also showed dieting to be associated with secondary amenorrhea regardless ED diagnoses [26]. This association was previously highlighted in a non-ED clinical population [27]. Dieting could determine absolute weight loss and decrease of fat mass contributing to impairments in hypothalamic-pituitary-ovarian function and in turn, leading to menstrual dysfunction.

Treasure et al., in an early study conducted in 1985 firstly described the changes in the ultrasonographic appearance of ovaries in women with AN during weight gain [28]. In the anorectic phase there seems to have a regression of hypothalamic-pituitary-gonadal function to a prepubertal stage. As long as the patients gain weight, there is a progression from amorphous

small ovaries to several small cysts from which one dominant cyst emerges leading to menses resumption. Weight restoration is therefore accompanied with a return to ovarian size to normal. These findings are confirmed in a more recent study [29] in which the authors found a positive correlation between increases in weight for height and BMI percentiles with the increases in grade of U/S appearance, being difficult to establish an arbitrary set weight due to individual variation. They concluded that pelvic U/S could be used to follow up changes in uterine and ovarian morphology as a function of weight gain.

In conclusion, whilst the hypothesis that amenorrhea is primarily due to low BMI or behavior influencing energy balance seems to be the most prevalent ones [8], the etiopathogenesis of amenorrhea in patients with AN could be more complexly related to multiple factors. It is commonly accepted that low BMI is a crucial mediator in the development of amenorrhea, but also the interplay between physical exercise, percentage of body fat, leptin levels, cortisol levels and comorbid symptoms could have an important role.

MENSTRUAL DYSFUNCTION, BULIMIA NERVOSA (BN) AND BINGE EATING DISORDER (BED)

Despite their normal weight, amenorrhea can occur in up to 40% of patients with BN [4] and it has a high prevalence in patients with BED [30]. Oligoamenorrhea, defined as irregular periods or spotting, occurs in 34% to 64% of women with bingeing behaviors [2]. Obesity, associated with up to a four-fold risk of menstrual dysfunction [31,32], is often comorbid with BED.

The relationship between obesity and menstrual dysfunction is complex, and androgen and estrogen alterations could have a role in its risk mechanisms. Sex Hormone Binding Globulin (SHBG), a protein carrier able to bind testosterone and estrogens with high affinity and lower affinity respectively, could also be implicated. Concentrations SHBG in the blood decrease as severity of obesity increases. Fat distribution also affects SHBG levels. Women who suffer from central adiposity have lower SHBG levels compared to females who have peripheral obesity [33]. Hence females with central obesity have a higher percentage of free testosterone fraction compared to those who have peripheral one. Adipose tissue has several endocrinological functions, including androgen production, inter-conversion of androgens into estrogens and viceversa, depending on the amount of fat [33]. The interplay between raised androgen production and reduced androgens binding to SHBG determines hyperandrogenism resulting in inhibition of follicular maturation and therefore an ovulation.

Hormones like insulin and insulin-like hormone factors have been shown to exert effects to an extent on reproductive events, such as ovarian steroidogenesis, folliculogenesis and ovulation physiology [34].

Similar mechanisms are responsible for the development of menstrual dysfunction in patients with BN. Eating binges are commonly characterized by a large amount of fat and carbohydrates.

Recurrent binge eating may decrease glucose tolerance with a consequent increase in circulating insulin levels leading to a raised testosterone production [34]. Likewise SHBG, Insulin-like hormone factor and the consequent increased testosterone levels play a key pathogenic role in the development of menstrual dysfunction [30].

Menstrual dysfunctions in BN could also relate to impairment in the Hypothalamus-Pituitary-Ovarian axis with a consequent low LH, FSH and estradiol levels [35]. Despite their normal weight, engaging in strict diet with the consequent sudden weight fluctuation typical of patients with BN can result in hormonal changes [35].

Polycystic Ovary Syndrome (PCOS), which is marked by menstrual disruption, has been demonstrated to be strongly associated with binge behaviors [36]. PCOS is a condition characterized by cysts in the ovaries, oily skin or acne and hirsutism as result of elevated serum level of testosterone. It was supposed that high testosterone levels may determine appetite alteration and consequently promote binge behaviors by food craving and impulse control [37]. In favour of this assumption, the use of flutamide, a testosterone antagonist, has been demonstrated to improve bulimic symptoms 1 week after the beginning of the treatment [38]. Ovaric cysts were maintained during the early stage of recovery but they resolved completely when normal eating behaviors pattern has been restored in the long-term [39].

A high prevalence of polycystic ovarian morphology, ranging between 76 to 100%, has been found in patients with BN when only ovarian morphology is studied through ultrasound [39]. When the PCOS diagnosis is assessed using clinical features, serum bio-markers and ultrasound, the prevalence of PCOS is 16.6% compared to 5-10% of the general population [37].

Sbaragli et al. found that BED was more frequent in infertile females than in controls and in “functional” female infertility and in women with PCOS than in anatomic female infertility or in controls [40]. In addition, almost 25% of people with PCOS meet criteria for BED [41].

Recently, Algars et al. found that women who had a lifetime binge eating were more likely to report amenorrhea or oligomenorrhea compared to women who had never engaged in this behavior, after controlling for compensatory behaviors like self-vomiting, laxative use and diuretic use, meaning that the risk to have menstrual dysfunction is similar in BN and in BED regardless of compensatory behaviors [30].

Compensatory behaviors, like self-vomiting, have also been found to be associated to menstrual dysfunction.

In a large survey study conducted in adolescent females, Austin et al., found a strong association between vomiting frequency and menstrual irregularities. In particular, girls who vomited once to three times a month in order to control their weight were two times more likely and girls who vomited once a week or more often were three times and a half more likely to experience menstrual dysfunction compared to females who were not engaged in this behavior [42]. The

association between vomiting and irregular menses has yet to be clarified, although some plausible risk mechanisms have been hypothesized. Both bingeing and vomiting have been found to be associated to a raised insulin secretion [43] which may mediate even hyperandrogenism in patients with BN, as explained above. Furthermore an association between menstrual irregularities, vomiting, opioids and dopamine activity was found. The emesis center is located in the medulla and works as a chemoreceptor trigger zone in the postrema area that is characterized by high-density opioids and dopamine receptors [42]. Increased opioids and dopamine activity is known to be involved in menstrual dysfunction [44] and a high frequency of vomiting may alter menstrual function by an increased opioids and dopamine release [45].

Although menstrual dysfunction seems to be a common problem in women suffering from BN or BED, research on why some females develop menstrual disturbances rather than others has been inconclusive. To date, many factors have been suggested to be involved in the physiopathogenesis of menstrual dysfunction however further research is needed in order to better understand these relationships.

COMPLICATIONS OF MENSTRUAL DYSFUNCTION

Several complications, in some cases not reversible, can accompany long-term menstrual dysfunction. Since the ED onset commonly occurs during adolescence, menstrual dysfunction can affect growth, peak bone mass acquisition, physical and cognitive development.

First of all, pubertal delay is quite common in patients with early AN onset [2]. In particular, Palla et al. found out that 17% of young female with AN had sexual maturity ratings that were 2 standard deviations below the mean for age [46]. Accordingly, Misra et al. found that 94% of premenarchal girls with AN versus 28% of premenarchal control subjects were above the mean age at menarche for white girls, and 35% of premenarchal AN girls versus 0% of healthy adolescents were delayed >2 standard deviations above the mean. In adolescent females who had attained menarche, 32% had menarche at an age greater than the mean age of menarche [47].

Also impaired growth trajectories have been found frequently in people with AN, possible due to a lack of estrogen secretion, which along with Growth Hormone (GH) and IGF-1, are fundamental for the normal development of bones [48].

In fact, another consequence of the low estrogen levels during adolescence is the failure in acquiring the peak bone mass [48]. Adolescents with AN have significantly decreased rates of bone accrual compared with controls [49], and these alterations may be permanent. Women with AN who develop AN during the adolescent years tend to have lower bone density than those who develop this condition in adult life, despite a similar duration of amenorrhea [50].

This might be explained by the strong anti-resorptive effect of estrogen which modulates the activity of certain cytokines with the aim of stimulating osteoblasts activity and of inhibiting osteoclasts one [51]. Bachrach et al. found that in a group of 18 patients with amenorrhea aged

between 12 and 20 years old, 12 had bone density superior than 2 standard deviations less than normal values for age. Most of the girls had received an AN diagnosis less than a year earlier [52]. This finding suggests that great deficits of bone mass are seen in young females with AN, even at the onset, as a results of amenorrhea.

AN has a profoundly deleterious effect on both cortical and trabecular bone compartments. Adolescent girls with AN were shown to have reductions in cortical thickness and cortical area, increased cortical porosity and decreased trabecular thickness compared with normal-weight controls [53]. Similarly, adult women with AN have reductions in trabecular number and thickness with increased trabecular separation [54,55].

Consistently with these studies, an increased fracture risk has been reported in both adults and adolescents with AN [56]. Recovery from AN is important in improving bone health. In adults with AN, studies have shown increases in bone density following weight gain and/or menstrual recovery [57].

On the other hand, oligomenorrhea appears not to have a strong impact on bone density in patients with BN [58].

Conflicting evidence exists in literature concerning fertility and reproductive health. Patients with ED are often able to conceive despite their severe menstrual dysfunction [59,60]. Nevertheless recent evidence suggest that lifetime ED is associated with fertility problems, unplanned pregnancies and negative attitude to pregnancy [61]. A recent study conducted in a large cohort of females suffering from ED have demonstrated that women with BN have a higher risk of induced abortion compared to controls while females with BED have a higher risk of miscarriage [59]. This means that to a certain extent menstrual dysfunction can severely affect reproductive health and infertility.

Lastly, menstrual dysfunction in adolescents with an ED can exert a significant impact on cognitive function. Research on brain changes in AN suggests that the development of an ED during childhood or adolescence may cause structural and functional alterations. It's still not certain whether these abnormalities are reversible or not [2].

Structural neuroimaging has shown increased Cerebrospinal Fluid (CSF) volumes associated with decreased total gray- and total white-matter volumes in adolescent females with AN. Weight-recovered patients showed persistent increase in CSF volumes and gray matter volume deficits compared to healthy controls [62].

Consistently, women with adolescent-onset AN were found to have larger lateral and third ventricles and showed a broad range of neuropsychological deficits compared with healthy control subjects. Both weight recovery and normalization of the cortisol levels were associated with the reversal of the structural brain abnormalities. However, women with persistent amenorrhea or menstrual irregularity showed cognitive function deficits in all tested domains, including recall, verbal memory, working memory, visual reproduction, reading, math, and oral language [63].

CONCLUSION

In conclusion, varying levels of menstrual dysfunction are present across all forms of eating psychopathology with different and complex mechanisms. Since the onset of ED occurs during adolescence, menstrual disturbances can be associated with permanent impairment in several body functions with consequent severe disabilities.

The clinical importance to assess menstrual dysfunction in patients who have a diagnosis other than AN is often overlooked. Therefore the importance of reproductive and endocrinological health counselling should be emphasized as well as periodical monitoring in patients with current or former ED in order to reduce the risk of fracture and unfavourable reproductive outcomes. Lastly, General Practitioners and gynaecologists should routinely assess for ED women presenting with menstrual dysfunction. Specific questions about ED should be required in order to detect dysfunctions early and to avoid severe complications.

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