

Review Article

Obstetric Complications of Anorexia Nervosa

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Submitted: 05 June 2023

Accepted: 05 July 2023

Published: 07 July 2023

ISSN: 2333-6439

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Keywords

- Anorexia Nervosa
- Amenorrhea
- Pregnancy
- Outcomes
- Bone mineral density

Abstract

The eating disorder, Anorexia Nervosa (AN), leads to a malnourished state and negatively impacts every system of the body. There are unique obstetric and gynecological concerns affecting females with this illness, and despite recent findings, several misconceptions persist. Among these is the fallacy that females with AN cannot get pregnant. Though many patients with AN experience amenorrhea, a considerable minority continue to retain their menses, and should be educated about the possibility of unplanned pregnancy. When pregnancy does occur, it is considered high risk, with increased likelihood of miscarriage, premature birth, and low birth weight infants. Patients with AN should be seen by a high-risk obstetric specialist and have a multidisciplinary team consisting of eating disorder experts including a registered dietician and a psychotherapist. Given their underweight status, a weight gain of 30-40 lbs is recommended. Contrary to previous thought, women who recover from AN do not have a greater risk for infertility, though resumption of menses can take up to 12 months. Though oral estrogen is beneficial to treat osteoporosis of post-menopausal women, oral estrogen is not beneficial for bone health in AN.

INTRODUCTION

Anorexia nervosa (AN) is a serious psychiatric illness characterized by dietary restriction leading to significant weight loss, with accompanying fear of weight gain, body dysmorphia, and over-valuation of weight on self-concept [1]. The disorder affects .3% - 1.9% of females and .1% - .3% of men [2,3], and has a mortality rate of approximately 5.1% per decade [4], which is the 2nd highest of all mental illnesses after opioid abuse [5]. Approximately 13% of individuals with AN die by suicide [6], with many more due to medical complications of hypokalemia, hypoglycemia, and cardiac abnormalities including bradycardia, abnormal heart rate variability, or increased QT dispersion [7]. There are two subtypes of AN: restricting anorexia nervosa (AN-R), with symptoms including deliberate food restriction and often accompanying over-exercise, and binge-eating/ purging anorexia nervosa (AN-BP) involving, in addition to food restriction, self-induced vomiting and/ or the abuse of laxatives or diuretics following subjective or objective binge eating episodes, or the mere intake of nutrition [1]. Patients present as malnourished, though it should be noted that atypical anorexia nervosa (AAN), classified under the Other Specified Feeding or Eating Disorders (OSFED) category of the Diagnostic and Statistical Manual of

Mental Disorders 5th Ed. Text Revision (DMV-5-TR), occurs when all criteria for AN are met, except despite significant weight loss, the individual's weight is still within or above the normal range [1]. Though AN can occur at any stage of life, onset is typically between the ages of 14 and 19 years in clinical populations, when puberty and body image concerns arise [8]. Rates of AN are increasing among girls ages 10-14 years and in women over 50, both considered sensitive periods involving reproductive hormone changes [3,9]. Anorexia nervosa and eating disorders in general are more likely to be experienced among sexual and gender minorities, a population that experiences unique concerns with regard to disordered eating and body image [10].

The causes of AN are multifactorial, and involve biological, psychological, and social factors. The illness is now definitely believed to be genetic, with heritability estimates ranging from 0.28 to 0.74 [11]. Metabolic mechanisms play a role in the development and persistence of the disorder and contribute to the extreme difficulty patients have of maintaining a healthy weight [12,13]. Neurobiological factors play a role in AN, with reward pathway abnormalities and cognitive rigidity impacting the preference for restriction, the formation of habits around restriction, and the ability to make meaningful changes in

behavior [14,15]. Psychologically, neuroticism and perfectionism are risk factors for AN [16], and the behavior of dieting has been implicated in the development of AN [17]. Sociocultural factors, such as the societal emphasis on the value of thinness, have contributed to historically increased rates of AN around the world, though AN can occur in the absence of Western influence [18]. Psychological comorbidities of AN include major depressive disorder, anxiety and obsessive-compulsive disorders, and substance use disorders [19].

Though AN can be an intractable illness, meaningful recovery is possible, with about 31% of patients with AN recovering in 9 years, and 68% within 22 years. [20] Early weight gain trajectories have been shown to predict higher rates of later remission [21]. Among adolescents with AN, Family Based Therapy (FBT), in which parents are empowered to align with each other in the service of feeding their child, is considered the gold standard of treatment [22,23]. While no single form of therapy has been found to be more effective than another among adults with AN [24], second and third-wave cognitive-behavioral therapy treatments such as Enhanced Cognitive-Behavioral Therapy (CBT-E) and Acceptance and Commitment Therapy (ACT) have been explored for the treatment of AN with some promise [25]. There are no designated psychiatric medications for the treatment of anorexia nervosa [26], however, the antipsychotic medication, olanzapine, may be effective in promoting weight gain among adults with AN [27]. Also, a variety of anxiolytic, antidepressant, and antipsychotic medications are utilized to treat common concomitant psychiatric issues. Repetitive Transcranial Magnetic Stimulation (rTMS) a form of electromagnetic neuromodulation can reduce AN symptoms and improve BMI, though more research is needed [28,29]. Ketamine is emerging as a novel treatment for AN and may promote neuroplasticity [30].

OBSTETRIC COMPLICATIONS

Approximately 75% - 85% of people with AN are amenorrheic [31]. This is caused by abnormalities at the level of the hypothalamic-pituitary axis (HPA) defined by a variable reduction in pulsatile hypothalamic gonadotropin-releasing hormone (GnRH) secretion and signaling to the pituitary gland, with reversion to a pre-pubertal state and resultant failure of ovulation. Amenorrhea was removed as one of the defining DSM criteria for AN, back in 2013, precisely because up to 25% of people, even with severe AN, continue to retain their menses. The variation in patterns of menstrual function with AN also was reason for removal of amenorrhea as a criterion for the diagnosis of AN.

Thus, many pregnancies, which occur during a bout of AN, are unplanned [32]. Therefore, females with AN should be educated that their amenorrhea does not preclude the chance of becoming pregnant from unprotected intercourse. Similarly, people with AN may also have oligomenorrhea due to fluctuations in their caloric intake, which may be sufficient to reverse the typical HPA alteration and cause ovulation to occur [33].

In general, the lower the body mass index (BMI), the greater

the possibility of amenorrhea [34]. A higher level of exercise also correlates with amenorrhea, likely mediated in part through low levels of leptin, which characterize AN, as a result of low-fat mass [35,36]. There are several other endocrine abnormalities which result from the weight loss and malnutrition of AN. These include elevated cortisol levels, decreased androgen levels, growth hormone resistance and the presence of the euthyroid sick syndrome [37].

One area of controversy in this regard is whether people with active AN have a lower fertility rate and once recovered, whether there remains a permanent reduction in rates of pregnancy. There is scant literature on the overall fertility rate during AN, but the prevailing sentiment is that fertility is impaired during active AN, which is certainly safest for the mother and a fetus. However, regarding the issue of residual infertility post recovery from AN, the pendulum has swung over the last 15 years. While in the past the myth propagated was that once someone has AN, even if they recover, that they will incur permanent infertility challenges, more recent studies have at least partially debunked that myth and there is no difference in rates of pregnancy post recovery [38,39]. Some of the uncertainty herein may emanate from the fact that women with AN are more likely to seek care from an infertility specialist, due to lingering doubts, but ultimately, they do not appear to have a greater risk for infertility.

Regardless, when active AN is present, pregnancy is considered to be high-risk. Therefore, the presence of active AN is thought to be a relative contraindication for pregnancy and for infertility treatments. The body image disturbances which define AN, will likely be exacerbated by the ongoing pregnancy. Although many patients subdue their food restriction and purging behaviors during the pregnancy, these behaviors return with ferocity in the puerperium [39]. Moreover, the pregnancy and lactation impose a tremendous stress on the maternal skeleton for mineralization of the fetal and newborn skeleton. Also, there is a greater reported incidence of premature birth, miscarriages, smaller head circumference, and low birthweight infants [40]. Rates of caesarean section may not be different among women with active AN and those without a history of AN [41].

Pregnancy for a woman with AN is a decision that should be made only post judicious deliberation. Referral to a high-risk obstetric specialist is critical along with assembling a multidisciplinary team consisting of a registered dietician (RD) and a therapist who are well-versed in the treatment of AN, due to this period of high physical and psychological vulnerability. Understandably, there are often concerns by the mother about her own body image, self-worth, and the need to put the fetus's needs above the desire to continue to engage in their own eating disorder [42]. As mentioned, some studies report remission of AN symptoms during pregnancy due to a sense of maternal responsibility for the health of their fetus [40]. There may however also be organic endocrine changes during pregnancy, such as increased placental production of dehydroepiandrosterone (DHEA), which promote remission of the AN during pregnancy [43]. While the specific dietary requirements for a pregnant lady

with AN are beyond the intended scope of this article, suffice it to say that the complexities of refeeding are increased due to a higher weight gain goal, greater caloric needs and a lack of specific guidelines for refeeding pregnant women with AN. Interestingly cohort studies have noted that pregnant women with AN may actually gain weight more quickly compared with those without AN [44]. Overall, given their underweight status, a weight gain of at least 30 – 40 pounds is recommended, with progressive increases of 350 – 450 calories per day in the second and third trimesters. Thankfully, it does not appear that the incidence of hyperemesis is greater in those with AN [45], although one study reported increased hyperemesis in people with AN [46]. Therefore, whether the pregnancy is unplanned or planned in the setting of AN, it is imperative that these people seek care from a multidisciplinary team with expertise in this area. As previously noted, this has import for optimizing fetal outcome as well as to protect the physical and psychological health of the expectant mother [47].

HORMONAL ISSUES

Given that the vast majority of women with AN are amenorrheic, questions often arise as to when resumption of menses can be expected to recur as the female progresses with weight restoration. There are only a paucity of studies which have rigorously investigated this question which is often of importance to patients to signify recovery or to inform weight goals. Most information seems to indicate that one needs to achieve their weight at the time when menses ceased or to reach about 93% of ideal body weight (a BMI of $> 19\text{Kg/m}^2$) [48,49]. However, there must also be emotional equanimity present. Yet, the periods do not return immediately with said weight gain, but commonly take up to twelve months after weight gain has been sustained [50].

For those patients who inquire about their menses as they reach weight gain goals, the oral progesterone challenge test can be used to demonstrate an underlying intact endocrine system. Moreover, oral contraceptive can be initiated to precipitate withdrawal bleeding as another marker of endocrine function. Leptin levels above $2\ \mu\text{g}$ are thought to predict resumption of menses along with higher estradiol levels [51]. Nevertheless, there is reticence to prescribe oral contraceptives in those recovering from AN because of tacit reliance on the birth control pills to also improve bone mineral density (BMD) which is well-known to be at risk due to the AN [52]. Although there is ample evidence for the beneficial effects of oral estrogen to treat the osteoporosis of post-menopausal women, there is strong evidence that oral estrogen is not beneficial for bone health in AN [53]. There do exist at least four credible alternative medicinal therapies for the treatment of low BMD in patients with AN [54].

CONCLUSION

In summary, AN is associated with many different aberrations in the endocrine system. Pregnancy complications are clearly a part of this group of changes because of the inherent malnutrition which is found in AN. However, there exist a number of

longstanding misconceptions about obstetrical issues in women with active AN. These can have deleterious effects on both the woman and their fetus. Weight restoration and resumption of menses seems to normalize these abnormalities and reduce future risk.

FUNDING

This research review was not supported by any grant or funding agency in the public, commercial, or not-for-profit sectors.

ACKNOWLEDGEMENTS

The authors wish to express our gratitude to providers and staff at Denver Health Hospital in Denver, CO, for their help and support in treating individuals with severe eating disorders.

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