Journal of Mind and Medical Sciences

https://scholar.valpo.edu/jmms/
https://proscholar.org/jmms/

ISSN: 2392-7674

Anorexia nervosa and reproduction: connecting brain to gonads

Mihaela Poterasu[1], David L. Rowland[2], Corina Ciobanu[3], Simona Fica[4]

[1]*Carol Davila University of Medicine and Pharmacy, Bucharest, Romania*
[2]*Valparaiso University, Department of Psychology, Valparaiso, Indiana, USA*
[3]*Obregia Clinical Hospital, Department of child and adolescent psychiatry, Bucharest, Romania*
[4]*Carol Davila University of Medicine and Pharmacy, Elias Clinical Hospital, Department of Endocrinology, Bucharest, Romania*

ABSTRACT

Anorexia nervosa (AN) is a psychiatric disorder that predominantly affects young women and is characterized by low caloric intake and a major dissatisfaction with one's body image. It is often overlooked and, while patients and family seek medical help, emaciation and nutritional misbalances may become extreme and potentially life threatening. Among the many somatic complications, an accumulation of early endocrine adaptations occurs, leading to functional amenorrhea and impaired reproduction as a result of dysfunction of the hypothalamic-pituitary-ovarian axis. Even though these conditions are reversible, long-term consequences may affect the fertility of women with AN and can lead to maternal and fetal complications during pregnancy and birth. This review presents the clinical particularities of reproduction in the context of AN, along with the possible pathophysiological mechanisms involved.

Category: Review

Received: September 27, 2019
Accepted: December 11, 2019

Keywords:

anorexia nervosa, reproduction, fertility, gonadotrophs, kisspeptin, leptin

***Corresponding author:**

Mihaela Poterasu, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
E-mail: mihaela06poterasu@gmail.com

Introduction

Anorexia nervosa (AN) is an eating disorder that consists of abnormally low body weight, a distorted perception of body image, and a fear of gaining weight [1]. Patients suffering from this condition have a major dissatisfaction with their body shape or size, and either perceive themselves as being fat despite extreme starvation, or become aware of their low weight but are in denial of its seriousness. The patients have a negative energy balance as a result of strict dieting or intense and extreme physical exercise [2].

Semantically, anorexia nervosa means the "neurotic loss of appetite," the condition being described as long as several centuries ago [3,4]. However, the diagnostic criteria for AN have changed substantially over time, being revised and redefined with each edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM). Although in current medical practice, the DSM-IV criteria are better known and applied, the most recent definition of AN dates to 2013 when DSM-5 removed the condition for amenorrhea from the diagnostic criteria, along with any threshold value for defining "low weight" [3,5]. Despite the fact that amenorrhea is common among patients suffering from AN, its assumption as a necessary element in the diagnosis algorithm of AN was limiting, as it did not take into consideration pre-pubertal or post-menopausal females, or females under contraceptive treatment. As a further matter, the DSM-IV definition was not inclusive of male patients, as their gonadal axis status was not taken into consideration [6,7].

Even though the actual diagnosis of AN is based solely on clinical judgment, the DSM-5 task force recommended using body mass index (BMI) for adults or corresponding BMI percentiles for adolescents in order to classify disease severity into four categories: mild (BMI>17kg/m2), moderate (BMI 16-16.99kg/m2), severe (BMI 15-15.99kg/m2), and extreme (BMI<15kg/m2). In addition, the disease is given two subtypes: restrictive AN and binge-eating/purging type, depending on patients' behavior and their attitudes towards dieting, exercising, or purging [5]. Last, the same task force defined atypical anorexia nervosa as a distinct eating disorder that encompasses all the features of typical AN, except low weight.

As expected, the more lenient definition of AN has led to an increase in its lifetime prevalence [8-10], which now reaches 4% [11,12]. It can affect both sexes, but is much

To cite this article: Mihaela Poterasu, David L. Rowland, Corina Ciobanu, Simona Fica. Anorexia nervosa and reproduction: connecting brain to gonads. *J Mind Med Sci*. 2020; 7(1): 1-8. DOI: 10.22543/7674.71.P18

more common among females, with a male-to-female ratio estimated to be 1:10. Even though it may occur at any age, its highest incidence occurs before the age of 20 years [5,13]. Its lifetime prognosis is good, although on a somatic level, the complications from emaciation, poor nutrition, or purging behavior may have long term effects. In addition, from a psychiatric perspective, relapses are possible, as well as association with other psychiatric diseases such as depression, anxiety disorders, social phobia, or obsessive-compulsive disorder [14]. According to several studies, approximately one fifth of all death causes of anorexic patients lies in suicide, which, along with medical disorders of the disease itself, raise the base mortality rate to 5% per decade [15,16].

Little is known about the etiology and triggers of AN, but genetic, environmental, and neurobiological factors seem to be involved [17]. Among the many metabolic complications, AN is characterized by an accumulation of endocrine adaptations such as acquired growth hormone (GH) resistance and subsequent low insulin-like growth factor (IGF1), chronic adrenal stimulation, euthyroid sick syndrome which, along with extreme starvation, is responsible for a further decrease in energy expenditure [3,18] and hypogonadotropic hypogonadism which leads to low trabecular score, impaired bone mineral density (BMD) [19], and functional amenorrhea. Considering that affected women are less likely to start a family and have children [20], this review addresses the issue of fertility and reproduction of females with a lifetime diagnosis of AN.

The aim of this review is, first, to provide an in-depth overview of the recent information regarding clinical and biological anomalies of reproduction in AN female subjects. A second objective is to define better clinical approaches regarding menstrual disturbances and pregnancy management in AN patients. Finally, we aim to identify less-explored pathophysiological mechanisms and potentially open new perspectives for further research in the near future.

A comprehensive search of the current literature on menstrual history, fertility and pregnancy, and birth outcomes related to AN was conducted via PubMed database in order to identify relevant studies published up to December 2019. We also included terminology for some of the biological and pathophysiological underpinnings of these clinical outcomes. For this purpose, we used a series of logical combinations of keywords and Medical Subject Headings (MeSH) terms, as follows: “anorexia nervosa”, “reproduction”, “fertility”, “pregnancy”, “kisspeptin”, “leptin”, “gonadotrophs”, “neurotransmitters,” and restriction to English language articles was made. No restriction was made on date or study type, but priority was given to recent clinical trials, although several relevant reviews or animal studies were included. An initial search identified 102 articles. We removed duplicates and considered for critical review only full text articles relevant to the topic, with 53 remaining articles included in our final analyses. To these, information from 14 additional articles or books was reviewed when documenting the epidemiology and general traits of anorexia nervosa. The present article is structured in two parts: in the first part we deal with the clinical aspects of reproduction in AN, and in the second part the mechanisms underlining them.

Discussions

Reproduction in the setting of AN

Optimal reproduction requires a mature and intact hypothalamic-pituitary-ovarian-axis, which in conditions of energy depletion and chronic stress can be difficult to achieve. Clinical studies investigating the effects of malnutrition and famine have shown that good reproductive capacity depends on adequate nutritional intake [21]. Furthermore, beyond the multiple somatic dysfunctions of anorexia, the sparse emotional availability of such patients leads to decreased libido and a rejection of sexual activity [22], which may also alter the odds of procreation. In this paper, we focus on clinical aspects that govern the reproduction and fertility of anorexic females.

Menstrual disturbances in anorexic females

From an evolutionary perspective, reproduction and growth are the first physiological processes to be sacrificed under conditions of intense stress that threaten survival. If anovulation is key to preservation, its clinical appearance can embrace different forms, from delayed or arrested puberty to menstrual irregularities or infertility, depending on the time of onset of AN, its duration, and severity. Consequently, females with AN can experience a wide range of menstrual disorders, such as anovulatory eumenorrhea, shortened or prolonged menses due to defects of follicular or luteal phases, premenstrual spotting, oligomenorrhea, or even amenorrhea [23].

Menarche is among the latter events in pubertal development and it follows thelarche and the rise of gonadal hormones by approximately 1.5-2 years. Evidence suggests that a weight loss of merely 10 to 15% from the normal weight-for-height can delay the age of menarche and sexual development [22,24]. A study conducted on a relatively large cohort of women (n=841) showed that 10% of anorexic females experienced primary amenorrhea, defined as a lack of menarche until the age of sixteen [24]. This same study emphasized the importance of age at onset of disease, because the vast majority of patients with primary amenorrhea experienced AN prior to the menarche and also reached the personal weight nadir at a younger age than patients with physiological menarche.

The same degree of weight loss of 10-15% from the normal weight seems to lead to a cessation of menstrual cycle in post-pubertal women as well [22,25]. So far, there

are no clear predictive factors for the resumption of menses. In 2013, Dempfle et al. showed that only half of amenorrheic patients resumed menses within one year from diagnosis, at a mean BMI of 19kg/m2 [26]. This finding is consistent with previous data showing that by one year from diagnosis, two thirds of anorexic females resumed menses, when they have reached either 90% of standard body weight for age and height, or were, in general, 2 kilos above the weight at which they stopped menstruating [27]. Other predictors for resumption of menses are body fat percentage, intensity of exercise, or even IGF1 levels (27–29) but, despite intense nutritional intervention, a large number of patients remained amenorrheic, highlighting that stress, anxiety, or psychological factors may play a role [8,13].

Fertility and fecundity

Fecundity is defined as the biological capacity to reproduce and is often indirectly assessed in epidemiological studies by measuring the rate of births, an index of fertility [30]. Power et al. showed that the fertility rate of patients with AN (defined as the mean number of children compared with that of the general population) is distinctly lower [31]. Moreover, results of a large longitudinal study describing the long-term outcome of AN found that only a quarter of anorexic patients became mothers at the time of follow-up, which is 2 to 3 times less than that of the general population [32].

Due to their menstrual impairment, females with AN are generally considered less fertile, and are, indeed, more likely to seek medical help regarding a fertility problem, but ultimately only women with both anorexia and bulimia nervosa are more likely to actually undergo treatment for infertility [33]. Eating disorders (ED) in general make individuals prone to infertility due to disruption of the hypothalamic-pituitary-ovarian axis and subsequent ovulatory dysfunction [34], but conflicting data exist [35] and clarifying studies are required.

It is clear that patients with ED are overrepresented in assisted human reproduction clinics [36] and, in 2014, Bruneau et al. reported that 8% of females visiting an infertility clinic met criteria for past AN, a rate higher than the prevalence in the general population [37]. They have a lower BMI than infertile patients without a lifetime diagnosis of AN and a higher level of anxiety [37]. Often their pathology is not recognized by trained infertility specialists [38], and even though precise guidelines for ED management regarding fertility treatment are missing, current recommendations involve inducing ovulation only in women with a minimum BMI of 18.5kg/m2 [23].

Nevertheless, it is still questionable to what extent their poorer fertility is due to ovulatory dysfunction. In the AVON Longitudinal Study of Parents and Children, 40% of females with AN admitted that their current pregnancy was unplanned, probably due to the misbelief that they were infertile [33]. Hence, it is more likely that anorexic females lack a stable partner and have ambivalent feelings towards pregnancy and motherhood, as reported in several studies [33,37,39], which may explain their lower fertility rate reported in literature.

Pregnancy and birth outcomes

Pregnant women with lifetime ED are at a higher risk to develop fetal and maternal complications and have poorer birth outcomes [40]. However, the evidence is conflicting, and while some studies note an increased risk for miscarriages, inadequate maternal weight gain during pregnancy, cesarean delivery, and small-for-gestational-age babies, or fetal distress [38,41], other studies suggest that the prognosis for pregnancy and birth for women with lifetime AN is approximately the same as for healthy subjects [42]. Watson et al. found an increased rate of cesarean delivery among patients ever having suffered from any ED [40], consistent with previous findings of Pasternak et al. [43]. Moreover, the birthweights tend to be slightly lower for children born to mothers who had AN [42-44], but, according to Micalli et al., this difference seems to be correlated with lower pre-gestational maternal BMI rather than with the disease itself [44]. Also, while women with a former diagnosis of AN have a lower, yet, within normal range BMI, their weight gain during pregnancy is actually higher than normally expected [41]. Regarding prematurity, AN alone does not predispose to a higher risk [40] than any other ED or to combined forms of AN and bulimia [41,43].

Going beyond the clinic

The biological mechanisms underlying the aforementioned clinical manifestations of AN remain uncertain. The literature on the role of neurotransmitters and hormones and their mechanisms of action is still limited, but recently, scientific evidence has yielded new insights. In the following sections, we detail some of the pathophysiological aspects relating reproductive anomalies to brain function.

Hypothalamic-pituitary-ovarian axis

The physiology of human reproduction in females is based on three functioning systems: the anterior hypothalamus where gonadotropin-releasing hormone (GnRH) is synthesized and secreted from the arcuate nucleus, the anterior pituitary that responds to GnRH by secreting follicle stimulating (FSH) and luteinizing hormone (LH), and the ovaries, that respond to the trophic action of the so-called gonadotrophins (FSH and LH) by producing estrogens through the menstrual cycle, progesterone in the luteal phase, as well as oocytes necessary for fertilization. The system auto-regulates by using a feedback mechanism, as estrogens signal at a

central level the availability of peripheral gonadal hormones and, thus, modulate GnRH secretion [45,46]. In sexually mature individuals, the release of GnRH follows a pulsatile pattern, generally every 60 to 90 minutes, leading to a rhythmic secretion of gonadotrophins [46].

Several studies have demonstrated that acute AN disrupts the normal functioning of the reproductive axis, and the pulsatile secretion of LH regresses to a prepubertal and immature pattern [18], especially when caloric restriction falls under 30kcal/kg/day [23]. As a result, GnRH suppression occurs, which then is manifested as hypothalamic amenorrhea [47]. On the one hand, GnRH suppression is directly responsible for the changes in LH amplitude and frequency pulses, which compromise the secretion of progesterone in thecal cells in the ovary. On the other hand, it lowers the secretion of FSH which alters the selection of the dominant follicle and thus diminishes the synthesis and secretion of estrogens [46]. Therefore, lower LH, FSH, and estradiol (E2) characterize the hormonal profile of anorexic patients [48] and positive correlations exist between the plasmatic level of these hormones and patient's BMI [49]. However, surprising data recently emerged showing that weight-recovered anorexic patients that were still amenorrheic had higher levels of sex hormones and gonadotrophins and better responses to pulsatile GnRH therapy than other women suffering from hypothalamic amenorrhea [50].

Last, the disproportioned sex distribution of AN predominating in women raises the hypothesis that, alongside its contribution to reproductive impairment, estradiol may also play an etio-pathogenic role, perhaps affecting satiety control and orexigenic peptides modulation [18].

Leptin

Leptin is an anorexigenic hormone secreted in adipose tissue, responsible for centrally signaling satiety and available energy deposits. It is now widely accepted that leptin modulates the activity of the reproductive axis by suppressing it in the case of an inadequate fat reservoir [51]. It plays a central role in metabolic control of fertility as it stimulates the hypothalamic expression of GnRH [52], even though specific leptin receptors in GnRH neurons are lacking. Compelling evidence suggests that kisspeptin is at the interplay between leptin and GnRH, and mRNA encoding leptin receptors have been found in the Kiss1 positive neurons of the arcuate nucleus [53]. Its connection to the hypothalamic-pituitary-ovarian axis is also shown by variations of its plasmatic concentrations during the menstrual cycle, as its level is slightly increased during the luteal phase and lower during the early follicular phase [52].

Furthermore, low levels of leptin, suggesting reduced fat mass, are associated with sexual immaturity [52] as it accompanies low LH secretion [23]. In line with this, in AN, as in all pathologies involving low fat mass, its level drops [54,55]. Interestingly and contrary to the general belief that leptin is a starvation hormone, in one study leptin was positively associated with appetite, suggesting that in individuals with AN, body weight regulation may be altered [55]. Experimental administration of exogenous leptin prevents stress-induced hyperactivity in anorexic patients, and even though leptin therapy is a potential regulator for resumption of menses, its use in AN is not feasible, as it decreases both appetite and adipose tissue [18].

Kisspeptin

Initially described two decades ago as a metastatic-suppressor factor of melanoma cells [56], after the identification of its receptor, kiss1R, kisspeptin was defined as a neuropeptide and assigned several endocrine and metabolic functions [57]. It is expressed in a variety of peripheral tissues within the gonads, placenta, small intestine, and pancreas, but its main site of action is located in the brain, specifically within hypothalamic neurons located in the arcuate nucleus (ARC) and the preoptic area, which corresponds to the rostral periventricular region of the third ventricle (RP3V) in rodents [45]. It plays a major role in reproduction as it facilitates the feedback mechanisms of the hypothalamic-pituitary-ovarian axis and triggers puberty initiation [58]. GnRH neurons lack requisite receptors for estradiol, but seem to have an affinity for kisspeptin, which mediates the dual feedback of the sexual hormones: negative feedback through ARC which is necessary for GnRH pulse generation, and positive feedback through RP3V which is necessary for LH pre-ovulatory surge [45]. Moreover, Millar et al. found that while kisspeptin may not be important in maintaining basal LH levels, it is, nevertheless, crucial for its pre-ovulatory stimulation [59].

Other than its role in reproductive function, kisspeptin also seems involved in inducing adequate reproductive behavior, as observed in animal studies [60], as well as modulating reactions to fear [61] and anxiety [62]. Outside the brain, among its increasingly identified roles, kisspeptin is involved in the implantation of the embryo, in the decidualisation of the endometrium and, by binding to its placental receptors, in the angiogenesis of the placenta [63]. As a further matter, by exploring its actions on metabolism, Tolson et al. showed that kisspeptin is involved in maintaining glucose homeostasis and weight [64].

The scientific evidence of kisspeptin variation in anorexia cases is yet sparse. However, given that food deprivation suppresses hypothalamic kiss1 mRNA [65], and that experimental administration of kisspeptin in women with functional hypothalamic amenorrhea

increased LH pulses [46], this neuropeptide may serve important functions. The few data available have shown a negative correlation between kisspeptin and intensity of exercise [66,67], but have failed to establish a connection with anxiety in AN patients [67]. An interesting finding reported by Bacopoulou is that menstruating females with atypical AN have higher levels of kisspeptin when compared to amenorrheic anorexic patients [49], suggesting that kisspeptin rises in order to keep a normal gonadal function.

Others

Many other neurotransmitters participate in the dynamics of reproductive regulation. To name a few, ghrelin, which is synthetized in the digestive system, is one of the most potent orexigenic hormones. It inhibits GnRH secretion and its concentration is diminished in AN patients [47]. Vasopressin, alongside its role in water reabsorption, is also involved in social behavior and sexual motivation [18], and even though its variation in anorexia is yet debatable, it also seems to stimulate adrenocorticotropic hormone (ACTH), which blunts functioning of the reproductive axis [66]. Last, there is controversy regarding the effects of oxytocin on anxiety, and while some authors report low levels in AN, interfering with empathy and attachment mechanisms, others consider it a potent anxiogenic factor that limits food intake of anorexic females [18,66].

Highlights

- ✓ Anorexia nervosa leads to functional amenorrhea and impaired reproductive function.
- ✓ Females with a lifetime diagnosis of anorexia nervosa are more likely to seek specialized medical help at infertility clinics.
- ✓ Pregnancy and birth outcomes of ever-affected women is controversial, but in the long term is rather good and similar to that within the general population.

Conclusions

Women with current AN have an impaired fertility status, but those who have recovered generally have, if desired and on a long term, a high chance for pregnancy and a good birth outcome. There are clear relationships between reproductive function and adipose tissue, nutritional status, intensity of physical exercises, and mental state. Although some of the underlying mechanisms for AN and reproductive anomalies are now being clarified, many hypotheses remain unexplored. To date, clinical trials regarding the dynamics of neurotransmitter involvement in the reproductive function of AN women is sparse, but a rising interest in the field will likely shed more light on the issue.

Abbreviations

"AN"=anorexia nervosa, "DSM"= Diagnostic and Statistical Manual of Mental Disorders, "BMI"= body mass index, "BMD"= bone mineral density, "GH"=growth hormone, "IGF1"=insulin-like growth hormone, "ED"= eating disorders, "GnRH"= gonadotropin releasing hormone, "FSH"= follicle stimulating hormone, "LH"= luteinizing hormone, "E2"= estradiol, "ARC"=arcuate nucleus, "RP3V"=rostral periventricular region of the third ventricle, "ACTH"= adrenocorticotropic hormone.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

References

1. Gay L, Satori N. Eating disorders. *Rev Infirm*. 2016;68(247):16–8.
2. Herpertz-Dahlmann B. Adolescent Eating Disorders: Update on Definitions, Symptomatology, Epidemiology, and Comorbidity. *Child Adolesc Psychiatr Clin N Am*. 2014;24(1):177–96. doi: 10.1016/j.chc.2014.08.003
3. Moskowitz L, Weiselberg E. Anorexia Nervosa/Atypical Anorexia Nervosa. *Curr Probl Pediatr Adolesc Health Care*. 2017;47(4):70–84. doi: 10.1016/j.cppeds.2017.02.003
4. Bemporad JR. Self-starvation through the ages: reflections on the pre-history of anorexia nervosa. *Int J Eat Disord*. 1996; 19(3): 217–237. doi: 10.1002/(SICI)1098-108X(199604)19:3<217::AID-EAT1>3.0.CO;2-P.
5. Cooper R. Diagnostic and statistical manual of mental disorders (DSM). Vol. 44, Knowledge Organization. 2013. Pp. 668–676.
6. Estour B, Marouani N, Sigaud T, Lang F, Fakra E, Ling Y, et al. *Differentiating* constitutional thinness from anorexia nervosa in DSM 5 era. *Psychoneuroendocrinology*. 2017; 84: 94–100. doi: 10.1016/j.psyneuen.2017.06.015
7. Estour B, Galusca B, Germain N. Constitutional thinness and anorexia nervosa: A possible misdiagnosis? *Front Endocrinol (Lausanne)*. 2014;5(OCT):1–5.

8. Mancuso SG, Newton JR, Bosanac P, Rossell SL, Nesci JB, Castle DJ. Classification of eating disorders: Comparison of relative prevalence rates using DSM-IV and DSM-5 criteria. *Br J Psychiatry*. 2015;206(6):519–20.
9. Caudle H, Pang C, Mancuso S, Castle D, Newton R. A retrospective study of the impact of DSM-5 on the diagnosis of eating disorders in Victoria, Australia. *J Eat Disord*. 2015;3(1):1–5. doi: 10.1186/s40337-015-0072-0
10. Mustelin L, Silén Y, Raevuori A, Hoek HW, Kaprio J, Keski-Rahkonen A. The DSM-5 diagnostic criteria for anorexia nervosa may change its population prevalence and prognostic value. *J Psychiatr Res*. 2016;77:85–91.
11. Brown TA, Holland LA, Keel PK. Comparing operational definitions of DSM-5 anorexia nervosa for research contexts. *Int J Eat Disord*. 2014;47(1):76–84.
12. Keski-Rahkonen A, Mustelin L. Epidemiology of eating disorders in Europe: Prevalence, incidence, comorbidity, course, consequences, and risk factors. *Curr Opin Psychiatry*. 2016;29(6):340–5.
13. Nicholls DE, Viner RM. Childhood Risk Factors for Lifetime Anorexia Nervosa by Age 30 Years in a National Birth Cohort. *J Am Acad Child Adolesc Psychiatry*. 2009; 48(8): 791–9. doi: 10.1097/CHI.0b013e3181ab8b75
14. Wild B, Friederich HC, Zipfel S, Resmark G, Giel K, Teufel M, et al. Predictors of outcomes in outpatients with anorexia nervosa – Results from the ANTOP study. *Psychiatry Res*. 2016;244:45–50.
15. Suokas JT, Suvisaari JM, Gissler M, Löfman R, Linna MS, Raevuori A, et al. Mortality in eating disorders: A follow-up study of adult eating disorder patients treated in tertiary care, 1995-2010. *Psychiatry Res*. 2013; 210(3): 1101–6. doi: 10.1016/j.psychres.2013.07.042
16. Suokas JT, Suvisaari JM, Grainger M, Raevuori A, Gissler M, Haukka J. Suicide attempts and mortality in eating disorders: A follow-up study of eating disorder patients. *Gen Hosp Psychiatry*. 2014;36(3):355–7. doi: 10.1016/j.genhosppsych.2014.01.002
17. Zipfel S, Giel KE, Bulik CM, Hay P, Schmidt U. Anorexia nervosa: Aetiology, assessment, and treatment. *The Lancet Psychiatry*. 2015;2(12):1099–111. doi: 10.1016/S2215-0366(15)00356-9
18. Støving RK. Mechanisms in endocrinology: Anorexia nervosa and endocrinology: a clinical update. *Eur J Endocrinol*. 2019;180(1):R9–R27. doi:10.1530/EJE-18-0596
19. Levy-Shraga Y, Tripto-Shkolnik L, David D, Vered I, Stein D, Modan-Moses D. Low trabecular bone score in adolescent female inpatients with anorexia nervosa. *Clin Nutr*. 2019; 38(3): 1166–70. doi: 10.1016/j.clnu.2018.04.013
20. Mustelin L, Raevuori A, Bulik CM, Rissanen A, Hoek HW, Kaprio J, et al. Long-term outcome in anorexia nervosa in the community. *Int J Eat Disord*. 2015; 48(7):851–9.
21. Sloboda DM, Hickey M, Hart R. Reproduction in females: The role of the early life environment. *Hum Reprod Update*. 2011;17(2):210–27.
22. Katz MG, Vollenhoven B. The reproductive endocrine consequences of anorexia nervosa. *BJOG An Int J Obstet Gynaecol*. 2000;107(6):707–13.
23. Gordon CM, Ackerman KE, Berga SL, et al. Functional Hypothalamic Amenorrhea: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2017;102(5):1413–1439. doi:10.1210/jc.2017-00131.
24. Lerman MA, Burnham JM, Chang PY, Daniel E, Foster CS, Hennessy S, et al. Primary amenorrhea in anorexia nervosa: impact on characteristic masculine and feminine traits. *Eur Eat Disord Rev*. 2014;40(8):1394–403.
25. Meczekalski B, Podfigurna-Stopa A, Katulski K. Long-term consequences of anorexia nervosa. *Maturitas*. 2013; 75(3): 215–20. doi: 10.1016/j.maturitas.2013.04.014
26. Dempfle A, Herpertz-Dahlmann B, Timmesfeld N, et al. Predictors of the resumption of menses in adolescent anorexia nervosa. *BMC Psychiatry*. 2013;13:308. doi: 10.1186/1471-244X-13-308.
27. Neville H. Golden, MD; Marc S. Jacobson, MD; Janet Schebendach, MA, RD; Mary V. Solanto, PhD; Stanley M. Hertz, MD; I. Ronald Shenker M. Resumption of menses in anorexia nervosa. *Fortschritt und Fortbildung der Medizin*. 1997;151:16–21.
28. El Ghoch M, Calugi S, Pellegrini M, Chignola E, Dalle Grave R. Physical activity, body weight, and resumption of menses in anorexia nervosa. *Psychiatry Res*. 2016; 246: 507–11. doi:10.1016/j.psychres.2016.10.043
29. Georgescu SR, Tampa M, Paunica S, Balalau C, Constantin V, Paunica G, Motofei I. Distribution of post-finasteride syndrome in men with androgenic alopecia; ESDR-Congress 2015, Journal of Investigative Dermatology (abstract) 135: S40, 2015.
30. Smarr MM, Sapra KJ, Gemmill A, Kahn LG, Wise LA, Lynch CD, et al. Is human fecundity changing? A discussion of research and data gaps precluding us from having an answer. *Hum Reprod*. 2017;32(3):499–504.
31. Power RA, Kyaga S, Uher R, MacCabe JH, Långström N, Landen M, et al. Fecundity of patients with schizophrenia, autism, bipolar disorder, depression, anorexia nervosa, or substance abuse vs their unaffected siblings. *Arch Gen Psychiatry*. 2013;70(1):22–30.
32. Fichter MM, Quadflieg N, Crosby RD, Koch S. Long-term outcome of anorexia nervosa: Results from a large

clinical longitudinal study. *Int J Eat Disord*. 2017;50(9):1018–30.
33. Easter A, Treasure J, Micali N. Fertility and prenatal attitudes towards pregnancy in women with eating disorders: Results from the Avon Longitudinal Study of Parents and Children. *BJOG An Int J Obstet Gynaecol*. 2011;118(12):1491–8.
34. Paslakis G, de Zwaan M. Clinical management of females seeking fertility treatment and of pregnant females with eating disorders. *Eur Eat Disord Rev*. 2019;27(3):215–23.
35. Rodino IS, Byrne S, Sanders KA. Disordered eating attitudes and exercise in women undergoing fertility treatment. *Aust New Zeal J Obstet Gynaecol*. 2016;56(1):82–7.
36. Cousins A, Freizinger M, Duffy ME, Gregas M, Wolfe BE. Self-Report of Eating Disorder Symptoms Among Women With and Without Infertility. *JOGNN - J Obstet Gynecol Neonatal Nurs*. 2015;44(3):380–8. doi: 10.1111/1552-6909.12573
37. Bruneau M, Colombel A, Mirallié S, Fréour T, Hardouin JB, Barrière P, et al. Desire for a child and eating disorders in women seeking infertility treatment. *PLoS One*. 2017;12(6):1–11.
38. Rodino IS, Byrne SM, Sanders KA. Eating disorders in the context of preconception care: fertility specialists' knowledge, attitudes, and clinical practices. *Fertil Steril*. 2017;107(2):494–501. doi:10.1016/j.fertnstert.2016.10.036
39. Micali N, Dos-Santos-Silva I, De Stavola B, Steenweg-De Graaf J, Jaddoe V, Hofman A, et al. Fertility treatment, twin births, and unplanned pregnancies in women with eating disorders: Findings from a population-based birth cohort. *BJOG An Int J Obstet Gynaecol*. 2014;121(4):408–15.
40. Watson HJ, Zerwas S, Torgersen L, Gustavson K, Diemer EW, Knudsen GP, et al. Maternal eating disorders and perinatal outcomes: A three-generation study in the Norwegian mother and child cohort study. *J Abnorm Psychol*. 2017;126(5):552–64.
41. Micali N, De Stavola B, Dos-Santos-Silva I, Steenweg-De Graaff J, Jansen PW, Jaddoe VWV, et al. Perinatal outcomes and gestational weight gain in women with eating disorders: A population-based cohort study. *BJOG An Int J Obstet Gynaecol*. 2012;119(12):1493–502.
42. Ekéus C, Lindberg L, Lindblad F, Hjern A, Eik-Nes TT, Horn J, et al. Birth outcomes and pregnancy complications in women with a history of anorexia nervosa. *Int J Eat Disord*. 2006;126(5):1134–43. doi:10.1016/j.ajog.2014.03.067
43. Pasternak Y, Weintraub AY, Shoham-Vardi I, Sergienko R, Guez J, Wiznitzer A, et al. Obstetric and perinatal outcomes in women with eating disorders. *J Women's Heal*. 2012;21(1):61–5.
44. Micali N, Simonoff E, Treasure J. Risk of major adverse perinatal outcomes in women with eating disorders. *Br J Psychiatry*. 2007;190(MAR.):255–9.
45. Harter CJL, Kavanagh GS, Smith JT. The role of kisspeptin neurons in reproduction and metabolism. *J Endocrinol.* 2018; 238(3): R173–R183. doi:10.1530/JOE-18-0108
46. Allaway HCM, Southmayd EA, De Souza MJ. The physiology of functional hypothalamic amenorrhea associated with energy deficiency in exercising women and in women with anorexia nervosa. *Horm Mol Biol Clin Investig*. 2016;25(2):91–119.
47. Paslakis G, Maas S, Gebhardt B, Mayr A, Rauh M, Erim Y. Prospective, randomized, double-blind, placebo-controlled phase IIa clinical trial on the effects of an estrogen-progestin combination as add-on to inpatient psychotherapy in adult female patients suffering from anorexia nervosa. *BMC Psychiatry*. 2018;18(1):93. doi:10.1186/s12888-018-1683-1
48. Estour B, Germain N, Diconne E, Frere D, Cottet-Emard JM, Carrot G, et al. Hormonal profile heterogeneity and short-term physical risk in restrictive anorexia nervosa. *J Clin Endocrinol Metab*. 2010;95(5):2203–10.
49. Bacopoulou F, Lambrou GI, Rodanaki ME, et al. Serum kisspeptin concentrations are negatively correlated with body mass index in adolescents with anorexia nervosa and amenorrhea. *Hormones (Athens).* 2017;16(1):33–41. doi:10.14310/horm.2002.1717.
50. Germain N, Fauconnier A, Klein JP, Wargny A, Khalfallah Y, Papastathi-Boureau C, et al. Pulsatile gonadotropin-releasing hormone therapy in persistent amenorrheic weight-recovered anorexia nervosa patients. *Fertil Steril*. 2017;107(2):502–9.
51. De Bond JA, Smith JT. Kisspeptin and energy balance in reproduction. *Reproduction*. 2014;147(3):R53–R63. Published 2014 Feb 3. doi:10.1530/REP-13-0509.
52. Tsatsanis C, Dermitzaki E, Avgoustinaki P, Malliaraki N, Mytaras V, Margioris AN. The impact of adipose tissue-derived factors on the hypothalamic-pituitary-gonadal (HPG) axis. *Hormones (Athens).* 2015;14(4):549–562. doi:10.14310/horm.2002.1649.
53. Motofei IG. A bihormonal model of normal sexual stimulation; the etiology of premature ejaculation. *Med Hypotheses*. 2001; 57(1): 93–95. doi: 10.1054/mehy.2001.1296
54. Eddy KT, Lawson EA, Meade C, et al. Appetite regulatory hormones in women with anorexia nervosa: binge-eating/purging versus restricting type. *J Clin Psychiatry*. 2015; 76(1): 19–24. doi: 10.4088/JCP.13m08753.

55. Haas V, Onur S, Paul T, Nutzinger DO, Bosy-Westphal A, Hauer M, et al. Leptin and body weight regulation in patients with anorexia nervosa before and during weight recovery. *Am J Clin Nutr*. 2005;81(4):889–96.
56. Lee JH, Welch DR. Identification of highly expressed genes in metastasis-suppressed chromosome 6/human malignant melanoma hybrid cells using subtractive hybridization and differential display. *Int J Cancer*. 1997;71(6):1035–44.
57. Hussain MA, Song WJ, Wolfe A. There is Kisspeptin - And Then There is Kisspeptin. *Trends Endocrinol Metab*. 2015;26(10):564–572. doi:10.1016/j.tem.2015.07.008
58. Tena-Sempere M. Kisspeptins and the metabolic control of reproduction: Physiologic roles and physiopathological implications. *Ann Endocrinol (Paris)*. 2010; 71(3): 201–2. doi: 10.1016/j.ando.2010.02.018
59. Millar RP, Roseweir AK, Tello JA, Anderson RA, George JT, Morgan K, et al. Kisspeptin antagonists : Unraveling the role of kisspeptin in Text reproductive physiology. *Brain Res*. 2010;1364:81–9. doi: 10.1016/j.brainres.2010.09.044
60. Hellier V, Brock O, Candlish M, Desroziers E, Aoki M, Mayer C, et al. Female sexual behavior in mice is controlled by kisspeptin neurons. *Nat Commun*. 2018;9(1):400. doi:10.1038/s41467-017-02797-2
61. Comninos AN, Dhillo WS. Emerging Roles of Kisspeptin in Sexual and Emotional Brain Processing. *Neuroendocrinology*. 2018;106(2):195–202.
62. Delmas S, Porteous R, Bergin DH, Herbison AE. Altered aspects of anxiety-related behavior in kisspeptin receptor-deleted male mice. *Sci Rep*. 2018;8(1):2–8. doi:10.1038/s41598-018-21042-4
63. Bhattacharya M, Babwah A V. Kisspeptin: Beyond the brain. *Endocrinology*. 2015;156(4):1218–27.
64. Tolson KP, Garcia C, Yen S, et al. Impaired kisspeptin signaling decreases metabolism and promotes glucose intolerance and obesity. *J Clin Invest*. 2014;124(7):3075–3079. doi:10.1172/JCI71075.
65. Merhi Z, Thornton K, Bonney E, Cipolla MJ, Charron MJ, Buyuk E. Ovarian kisspeptin expression is related to age and to monocyte chemoattractant protein-1. *J Assist Reprod Genet*. 2016;33(4):535–43.
66. Pałasz A, Janas-Kozik M, Borrow A, Arias-Carrión O, Worthington JJ. The potential role of the novel hypothalamic neuropeptides nesfatin-1, phoenixin, spexin and kisspeptin in the pathogenesis of anxiety and anorexia nervosa. *Neurochem Int*. 2018;113:120–136. doi:10.1016/j.neuint.2017.12.006.
67. Hofmann T, Elbelt U, Haas V, Ahnis A, Klapp BF, Rose M, et al. Plasma kisspeptin and ghrelin levels are independently correlated with physical activity in patients with anorexia nervosa. *Appetite*. 2017;108:141–50. doi:10.1016/j.appet.2016.09.032