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Hypothalamic Amenorrhea and the Long-Term Health Consequences

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Abstract

The menstrual cycle is a reproductive vital sign and provides insight into hormonal imbalance as well as pregnancy. The significance of estrogen, however, extends beyond fertility and plays a role on tissues and organs throughout the body. Functional hypothalamic amenorrhea is a common form of secondary amenorrhea resulting in estrogen deficiency in young premenopausal women. While reversible, the cause of this disorder is related to psychological stress, excessive exercise, disordered eating or a combination of these factors resulting in suppression of the hypothalamic–pituitary–ovarian axis. The resulting loss of estrogen has profound effects on many systems throughout the body including cardiac, skeletal, psychological and reproductive. Often, these young women are the 'walking well' as they do not have bothersome symptoms of low estrogen and are unaware of the consequences of estrogen deficiency. This review focuses on the health consequences of hypothalamic amenorrhea, current research and available treatment options.

Keywords

amenorrhea; estrogen; cardiovascular; premenopause

INTRODUCTION

The impact of estrogen deficiency has been extensively studied in menopause, however the impact of estrogen deficiency in young women lacks attention. Menopausal women have an increased risk of cardiovascular disease (CVD) due to the unfavorable shift of risk factors such as cholesterol and blood pressure resulting from low estrogen.[1] Bone health is also impacted as the most rapid amount of bone loss occurs the first year after menopause.[2] Menopause and low estrogen levels can also interrupt overall mental health with increased rates of depression and anxiety.[3] While these consequences have been well-studied in the menopausal woman, a similar phenomenon occurs in young premenopausal women with secondary amenorrhea due to estrogen deficiency. This review will focus on the cardiovascular, skeletal, psychological and reproductive impact of hypoestrogenemia in premenopausal women and discuss possible treatment interventions.

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ESTROGEN DEFICIENCY IN PREMENOPAUSAL WOMEN

One of the top causes of secondary amenorrhea is functional hypothalamic amenorrhea (FHA) which results in severe hypoestrogenemia and cessation of the menstrual cycle. Three main types of FHA are psychological stress, intense exercise, and disordered eating, making this a relevant women's health issue. According to the American Society of Reproductive Medicine, FHA is responsible for 20–35% of secondary amenorrhea.[4] It is estimated that FHA effects about 1.62 million women between the ages of 18 and 44 years in the US and 17.4 million women worldwide.[5–7]

The mechanism of FHA is due to suppression of gonadotropin releasing hormone (GnRH) in the hypothalamic-pituitary-ovarian axis resulting in low follicle stimulating hormone (FSH) and luteinizing hormone (LH) being released from the anterior pituitary.[8] Due to this impaired feedback mechanism, the ovarian granulosa cells do not receive a signal to produce estradiol. Therefore, endometrial thickening does not occur during the follicular phase resulting in amenorrhea in an otherwise healthy woman. The diagnosis of FHA is defined as amenorrhea for at least 3 consecutive months, with estradiol (E2) <50 pg/ml, FSH<10 mIU/ml, and LH<10 mIU/ml with the exclusion of other etiologies including anatomic and other pathologies such as thyroid dysfunction, hyperprolactinemia, premature ovarian insufficiency (POI), and polycystic ovary syndrome.[9] While this condition is reversible, the diagnosis is a diagnosis of exclusion. Importantly FHA is a condition that occurs during the peak of a woman's reproductive years, resulting in anovulation and infertility.

CARDIOVASCULAR CONSEQUENCES

Cardiovascular disease remains the leading cause of death in women in the United States. Recent data indicate that CVD death rates are *increasing* in premenopausal women while decreasing in both postmenopausal women as well as men.[10] The traditional risk factors for heart disease such as age, blood pressure, diabetes and cholesterol are not adequately predicting CVD risk in young women, leaving a significant amount of risk unexplained. Estrogen in a healthy blood vessel is a potent vasodilator via nitric oxide production. At the vascular level, estrogen-mediates inflammation, oxidative stress and over long-term estrogen increases endothelial-cell growth and inhibits smooth muscle cell proliferation. While there is much known about the cardiovascular impact of estrogen loss on postmenopausal woman, little is known about the impact on young, premenopausal women.

Animal data in cynomolgus monkeys has established that premenopausal CVD is strongly determined by estrogen status characterized by hypoestrogenemia.[11] Specifically, when young premenopausal monkeys are subjected to environmental stress due to frequent cage rotation and constant re-establishment of social hierarchical position; they develop a stress reaction that is characterized by a reduction of the central brain hormones that stimulate the ovaries, reproducing FHA.[12] Menstrual cycling becomes irregular or ceases, fertility is low or absent, and estrogen levels fall due to ovarian shut down. The monkeys have abnormally low FSH and LH, as well as low E2 and progesterone levels.[12] These young estrogen deficient monkeys subsequently develop abnormal coronary vasomotion and atherosclerosis as measured in the iliac artery, a 'surrogate' for the coronary arteries.[13] In addition, the

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female monkeys that maintain normal ovarian function and estrogen levels are protected from CVD. These results suggest strongly that environmental stress is a cause of amenorrhea and infertility among monkeys, and that the resulting estrogen deficiency can cause CVD. Furthermore, maintaining estrogen levels by administering oral contraceptive therapy to premenopausal monkeys for a 2-year period was found to be protective against the development of atherosclerosis in at-risk monkeys.[13]

Several lines of clinical evidence also link hypoestrogenemia in young women to premature CVD. An early clinical sign of hypoestrogenemia is menstrual cycle irregularities. Prior research from the Nurses' Health Study of over 82,000 women that self-reported menstrual cycle history demonstrated that the more irregular the menstrual cycle in young women the greater the risk for future CVD events; up to a 50% increase.[14] Menstrual cycling irregularities have also been associated with uterine atherosclerosis which lead to early menopause.[15] Early menopause, defined as menopause ≤45 years old, is associated with accelerated atherosclerosis and a two and a half fold increased risk of CVD compared to age-matched premenopausal women (95% CI 2.05–3.35).[16–18,19,20]

Genetic conditions that results in severe estrogen deficiency include Turner's syndrome, 45 X, and primary ovarian insufficiency, 46, XX. Turner's syndrome is an X-chromosomal defect that results in ovarian dysgenesis and lifelong estrogen deficiency and associated with a reduced life expectancy with the main cause of death being cardiovascular complications including a seven-fold higher rate of CVD.[21] Additionally, women with Turner's syndrome have higher rates of hypertension, hyperlipidemia, diabetes, and obesity. In a cross-sectional study of women in their early 30's, women with either Turner's syndrome or primary ovarian insufficiency had a significantly thicker carotid intimal medial thickness (CIMT), a marker of subclinical atherosclerosis, compared to normal controls of similar ages. (0.61 ± 0.07 mm; 0.60 ± 0.05, and 0.55 ± 0.06, $p<0.001$, respectively).[22]

The Women's Ischemia Syndrome Evaluation (WISE) studied women undergoing a clinically-indicated coronary angiogram as part of their regular medical care for chest pain symptoms or suspected myocardial ischemia.[23] In 95 premenopausal women enrolled, women were evaluated for hypothalamic hypoestrogenemia defined as estradiol <184 pmol/l (50 pg/ml), FSH < 10 IU/L, and luteinizing hormone <10 IU/L. Thirteen premenopausal women with CVD had significantly lower estradiol, bioavailable estradiol, and FSH (all $p < 0.05$), compared to the 82 premenopausal women without angiographic CVD, even after controlling for age. Estrogen deficiency was significantly more prevalent among the women with CVD compared to those without (69% vs 29%, respectively, $p=0.01$). In statistical modeling, estrogen deficiency was found to be the most powerful predictor of angiographic CVD.

BONE CONSEQUENCES

Estrogen deficiency significantly effects bone status and serves as a key factor in regulating adequate bone metabolism in the skeletal system.[24] By stimulating osteoblast (bone-building) activity, estrogen promotes the formation of certain growth factors including transforming growth factor beta (TGF-β), insulin-like growth factor 1 (IGF-1), and bone

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morphogenetic protein 6 (BMP6).[24] However, in estrogen-deficient women, such as those with FHA, bone production is suppressed due to osteoblast apoptosis, which results in diminished growth factor production.[25] In turn, the absence of estrogen promotes osteoclast (bone-resorption) activity by decreasing osteoprotegerin gene expression, which prevent the inhibition of osteoclast formation.[24] The rise in osteoclasts further increases the formation of RANKL (receptor activator of nuclear factor kappa B ligand), macrophage-colony stimulating factor (M-CSF), interleukin-6 (IL-6), interleukin-1 (IL-1), and tumor necrosis factor-α (TNF-α) which further leads to bone deterioration.[24] The loss of estrogen resulting from FHA poses a serious risk to young women for developing osteopenia or osteoporosis at an early age and over a lifetime.

Bone mineral density (BMD) uses x-rays to determine the amount of mineral in the bones, including calcium the primary structural element of bone density and serves as a measure of bone strength.[26] The connection between estrogen and calcium absorption is most noted in the intestinal tract. Hypoestrogenemia negatively impacts the absorption of calcium through the intestine thereby decreasing the availability of calcium for bone reabsorption.[27] Without calcium available, the cascade of bone loss in women with FHA continues.[27]

Reduced BMD due to low estrogen results in diffuse bone loss seen in the trabecular (spongy) bone underscoring the severity of FHA on the skeletal system.[24] It is estimated the mean BMD of a young women with only six months of hypoestrogenemia is equivalent to that of a woman 51.2 years of age.[28] The timing and duration of amenorrhea is also important with respect to the amount of bone loss. In a prior study of 24 women with FHA compared to 31 normal, age-matched women, 83% were diagnosis of osteopenia. Notably, the more severe osteopenia was found in the women with prolonged amenorrhea, however the most profound decline in BMD occurred early after onset of amenorrhea.[29, 30] This study highlights the similarity of the bone loss that occurs the first year in post-menopausal women, reiterating the importance of maintaining estrogen levels in premenopausal women.

Women with FHA have also been found to have higher cortisol levels in both the cerebrospinal fluid and peripheral circulation than eumenorrheic women.[31–33]In one study of 19 women with hypothalamic amenorrhea, 30 women with anorexia nervosa, and 30 eumenorrheic age-matched controls, urine free cortisol was inversely related to osteocalcin, a marker of bone formation, concluding that elevated cortisol levels leads to bone loss ($p=0.03$).[34] Consequentially, cortisol dysregulation severely impacts bone health through several mechanisms. Elevated cortisol has been associated with an imbalance in vitamin D absorption and metabolic-related hormones such as parathyroid and thyroid hormones, which are essential for maintaining normal BMD.[35, 36] Hypercortisolemia can lead to a decrease in osteoblast activity and inhibits intestinal calcium absorption due to the increased secretion of parathyroid hormone.[36]

Hypothalamic amenorrhea also results in hypothyroidism by suppressing thyroidal axes, which effects the basal metabolic rate. Particularly, triiodothyronine (T3) and thyroxine (T4) are reduced in women with FHA while TSH levels are uneffected.[31] Hypothyroidism impairs bone formation and growth retardation due to the negative effect of thyroid deficiency on bone metabolism.[37] The rate of bone formation is decreased by 50% while the

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rate of bone resorption is decreased by 40%, leading to a greater amount of bone loss.[38] In turn, amenorrheic athletes experience constant metabolic alterations and energy deficits due to greater energy expenditure and caloric restriction from these various factors.[31] These metabolic disturbances including hypercortisolemia, hypoleptinemia, and hypothyroidism may have immediate and long-term effects on bone health.

The term “female athlete triad” is a syndrome used to describe a type of FHA with three interrelated conditions: amenorrhea, osteoporosis, and disordered eating.[39] These components are becoming increasingly prevalent among competitive female athletes, especially among those who participate in strenuous sports where leanness is highly encouraged such a competitive runners and swimmers.[39] After the passing of Title IX of the Educational Amendments Act in 1972, the term female athlete rose in popularity as more women took part in routine exercise.[31] In one study comparing 669 female athletes to 607 nonathlete controls, athletes reported more stress-related fractures and menstrual irregularities compared to nonathletes ($p<0.05$).[39] Despite the fact that these at-risk factors have been frequently observed in women trying to excel in their sports, the female athlete triad remains an under-recognized concept, which puts more women with these factors at greater risk of worsening their symptoms if they are not detected early. Therefore, more awareness is needed to expose the detrimental impact of excessive exercise, stress, and disordered diet on bone status.

PSYCHOLOGICAL IMPACT

While psychological stress can result in FHA, this relationship is bidirectional, in that FHA greatly impacts the psychological status of effected individuals. Women with FHA have significantly higher depression scores, greater anxiety, and increased difficulty coping with daily stress as compared to healthy controls ($p<0.05$).[40] Despite increased anxiety and depressive traits these women fail to seek professional help once they experience menstrual irregularities. Increased stress is also associated with higher cortisol levels and serves as a likely mediator of mood impairments, leading to a large array of psychiatric symptoms like anxiety and depression.[35] According to one study of 21 healthy controls, 18 amenorrheic women with anorexia nervosa, and 13 normal-weight women with FHA, cortisol levels showed a strong correlation with anxiety and depressive symptomology based on the Hamilton Rating Scale for Anxiety (HAM-A) and Depression (HAM-D) ($p=0.002$).[35] The link between disordered mood and hypercortisolemia is complex, however recent findings have shown that stress disrupts the GnRH neural network, which in turn suppresses the GnRH drive.[40]

Women with FHA also have more dysfunctional attitudes such as perfectionistic behavior and extra attention to the judgments of others in comparison to their eumenorrheic counterparts.[41] For instance, amenorrheic women generally express greater concern for their physical appearance and fear of gaining weight, both which impacts eating habits and stress. In one such study that included 8 women with FHA and 8 women with normal menstrual cycles, FHA patients exhibited markedly different dietary habits from the reference controls and consumed 50% less fat ($p<0.001$), twice as much fiber intake ($p<0.05$), and more carbohydrates ($p<0.05$) due to their intensified desire for thinness and depressed mood.[42] A

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high rate of eating disorders such as binge eating has also been noted in women with FHA due to their psychological fixation on physical appearance. In a study with 95 amenorrheic women, 41% suffered from an eating disorder with 27% specifically experiencing binge eating disorder.[43] In addition to these external concerns, FHA women also report greater internal feelings of insecurity, inadequacy, and lack of control over their lives.[40] While the exact mechanism of mood disturbance in FHA remains unknown, there is significant overlap between metabolic factors and psychosocial stressors that work synergistically to bring about FHA.[40]

The effect of FHA on mood and other psychological traits is linked to sex steroid levels, most importantly estrogen.[44] Various fluctuations in neuropeptides and neurotransmitters are related to hypoestrogenemia in women with FHA. The presence of estrogen influences many areas of the brain including to the hypothalamus, cerebellum, nigrostriatal and mesolimbic system, amygdala, hippocampus, cerebral cortex, and brainstem.[45] In turn, cognitive behavior and mood modulation are impacted. Many neurotransmitter and neuromodulator systems are also effected including fluctuations in the production of serotonin and dopamine, which both serve as neurotransmitters that regulate mood.[45] Specifically, low serotonin and dopamine levels in the brain give rise to the onset of depression.[46] Estrogen further modulates a variety of neurotransmitters including serotonin, acetylcholine, dopamine, and norepinephrine.[47] Animal models have demonstrated that changes in estrogen directly effect serotonin transmission, binding, and metabolism in the cognitive regions of the brain.[47] Human data further support the role of estrogen and its impact on serotonin, as estrogen increases cortical 5-HT_{2A} binding, serotonin receptors, thereby influencing emotion regulation and cognitive function.[47]

FERTILITY CONSEQUENCES

It is important to recognize that FHA is a condition that occurs during peak reproductive years, resulting in anovulation and infertility. Often, these young women are the ‘walking well’ as they do not have bothersome symptoms of low estrogen and are unaware of the consequences of estrogen deficiency. During routine, well-women exams, the diagnosis can also be overlooked and usually not made until a woman is attempting pregnancy. Health care providers should to understand the impact of FHA and educate women about the repercussions on future fertility.

The hypothalamic dysfunction associated with FHA results in decreased or inhibited GnRH secretion, which effects the pulsatile release of pituitary gonadotropins, LH and FSH, resulting in estrogen deficiency and anovulation.[31] Without the presence of estrogen, the ovary cannot stimulate follicles, nurture an ovum, and release it from the ovary into the fallopian tube for fertilization. Endometrial thickening is also prevented as the lack of cyclical changes of estradiol and progesterone concentrations leads to abolished endometrial lining.[48] Anovulation is a major characteristic of FHA, so patients with this condition are unable to become spontaneously pregnant.

While this condition is a reversible cause of secondary amenorrhea, untreated and prolonged FHA can impact reproductive health. The disorder can lead to atrophic changes in the

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urogenital mucosa and in the muscles of the uterus.[49] The estrogen deficiency of FHA parallels that which is seen in postmenopausal women. The earliest sign of estrogen deficiency is decreased vaginal lubrication, followed by other vaginal and urinary symptoms that may be exacerbated by superimposed infection.[50] The thinned endometrium and increased vaginal pH level predispose the genitourinary tract to infection and mechanical weakness.[50]

Even though few studies directly address FHA and subsequent pregnancy with birth complications, there is research that concludes psychological stress and low BMI increase the chance of high-risk delivery. It is common for FHA women to present a low body mass index while attempting pregnancy. Low BMI is directly linked to an increased risk of miscarriage and preterm delivery in both women who become pregnant spontaneously and after fertility treatment.[51, 52] In a study of 603 women whose most recent pregnancy had ended in first trimester miscarriage (<13 weeks gestation) and 6,116 women whose most recent pregnancy had progressed beyond 12 weeks, it was found that underweight (BMI < 18.5) women were 72% more likely to miscarry in the first trimester.[53] Additionally, in a German study, low BMI was one of the main risk factors for preterm delivery defined as delivery prior to 37 weeks gestational age.[52]

The psychological health of a mother plays an important role in fetal development. One study of 865 pregnant women that were interviewed three times over the duration of their pregnancy found that low birth weight and prematurity were a direct result of maternal distress.[54] Results have also concluded that healthy eating, reduced stress, and improved emotional wellbeing help women in early pregnancy to decrease their risk of miscarriage.[53] These causes for miscarriage and preterm labor are important for the FHA woman whose amenorrhea is due to stress, excessive exercise, and disordered eating.

TREATMENT OPTIONS

The aim of FHA treatment is to re-establish a regular ovulatory menstrual cycle. The choice and success of treatment depends upon the ability to identify the correct etiology: psychological stress, excessive exercise, or disordered eating. However, it is not uncommon for a woman to have more than one of these overlapping factors.

Most women who present to the medical provider with a diagnosis of FHA are prescribed oral contraceptive therapy (OCP). While the use of OCPs is an estrogen replacement and will provide a withdrawal bleed, it is not intended to support the resumption of normal endogenous hormone activity. The underlying etiology of the FHA still needs to be addressed. Studies have not shown support for the use of OCPs to prevent further bone loss associated with FHA, as changes in BMD and BMC are unrelated to their use.[64] Therefore, OCPs should not be thought of as a treatment option to prevent further bone loss or to return a healthy menses.

Cognitive behavioral therapy (CBT) is a successful treatment option for FHA due to psychological stress and results in resumption of ovarian activity. In one study, 16 women with FHA were randomized to 16 CBT sessions or observation over a 20-week period.

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[55]Among women that received CBT, 7 (87.5%) resumed ovarian activity compared to 1 (12.5%) in the observation group.[55] Furthermore, CBT restored estradiol and progesterone levels over the 20 week period. In another study, CBT lowered cortisol levels, and increased leptin and TSH levels in women with FHA.[56] These results provide evidence of a connection between the metabolic and psychologic domains. Success from CBT underscores the need in FHA women to alter patterns of thinking and behavior as well as a non-medication alternative for treatment. Future studies should focus on the long-term impact of CBT and FHA.

Leptin, an adipose-derived hormone, is recognized as a mediator of energy intake and expenditure and greatly influences body weight by regulating appetite and metabolism.[57] In women with FHA, low leptin levels are due to decreased fat mass leading to a reduction in GnRH secretion and hormonal imbalance.[58, 59] Leptin replacement therapy, administered as subcutaneous recombinant methionyl human leptin (r-metHuLeptin) twice daily for 2–3 months in women with FHA was found to increase markers of bone-formation, suggesting that leptin plays a role in bone density.[59] Leptin replacement therapy also resulted in follicular growth and ovulation as well as increasing circulating estradiol, LH, and thyroid hormone.[59]

The treatment for anovulatory infertility associated with FHA is hormonal based. For women with FHA, induction agents typically used for anovulation do not work without proper hypothalamic function and require sufficient levels of endogenous estrogen. Consequently, clomiphene citrate and letrozole are not ideal options for these women. Human menopausal gonadotropin (HMG) is a combination of LH and FSH and as an injection will stimulate ovaries to induce ovulation. As with all ovarian stimulation hormones, there is risk of multiple pregnancies and hyperstimulation syndrome.[60] Several studies also report ovulation and pregnancy after intermittent subcutaneous low-dose pulses of GnRH in women with presumed GnRH deficiency.[61] Although this treatment provides an effective and physiologic method of restoring reproductive function in FHA and minimizes the chance of multiple pregnancy, the GnRH pump is currently unavailable in the US and clinical trials are ongoing.[61] Kisspeptin, a principal regulatory protein important for initiating secretion of GnRH, has been studied in smaller pilot samples as an intravenous infusion however it is also not clinically available and more research is needed to demonstrate LH pulsatility.[62] For these reasons, most physicians discuss in vitro fertilization as a safer and effective treatment option. In a study of 27 FHA patients, 81.8% of menstrual cycles initiated with recombinant FSH and HMG with GnRH agonist, proceeded to embryo transfer.[63] Despite unexpectedly high spontaneous loss and multiple pregnancy rates, there was a fertilization rate of 57.6%.[63]

CONCLUSION

Hypothalamic amenorrhea is a prevalent disorder in young women that occurs at the peak of reproductive life. While it remains a diagnosis of exclusion, medical professionals should be aware of the long-term health consequences of low estrogen levels that go beyond the reproductive system. Hypoestrogenemia in young women has been associated with abnormal vascular function and premature CVD. Similar to recently postmenopausal women, women

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with FHA can begin to experience bone loss in as little as six months of amenorrhea, leading to premature osteoporosis. Women with FHA are further susceptible to anxiety and depressive traits, yet unaware of the connection, young women fail to seek professional help once they experience menstrual irregularities. While several treatment options have been explored, more research and awareness is needed in this important area of women's health.

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References

1. Stevenson JC, Crook D and Godsland IF. Influence of age and menopause on serum lipids and lipoproteins in healthy women. Atherosclerosis. 1993;98:83–90. [PubMed: 8457253]
2. Riggs BL, Khosla S and Melton LJ. A unitary model for involutional osteoporosis: estrogen deficiency causes both type I and type II osteoporosis in postmenopausal women and contributes to bone loss in aging men. Journal of bone and mineral research. 1998;13:763–773. [PubMed: 9610739]
3. Elavsky S and McAuley E. Physical activity and mental health outcomes during menopause: a randomized controlled trial. Annals of Behavioral Medicine. 2007;33:132–142. [PubMed: 17447865]
4. Medicine PCotASfR. Current evaluation of amenorrhea. Fertility and sterility. 2004;82:33–39.
5. Pettersson F, Fries H and Nillius SJ. Epidemiology of secondary amenorrhea: I. Incidence and prevalence rates. American journal of obstetrics and gynecology. 1973;117:80–86. [PubMed: 4722382]
6. Bureau C Statistical Abstract of the United States, 2010: Government Printing Office; 2009.
7. McDevitt TM. World population profile: US Government Printing Office; 1996.
8. Vadakkadath Meethal S and Atwood CS. The role of hypothalamic-pituitary-gonadal hormones in the normal structure and functioning of the brain. Cellular and molecular life sciences: CMLS. 2005;62:257–70. [PubMed: 15723162]
9. Bairey Merz CN, Johnson BD, Sharaf BL, Bittner V, Berga SL, Braunstein GD, Hodgson TK, Matthews KA, Pepine CJ, Reis SE, Reichek N, Rogers WJ, Pohost GM, Kelsey SF and Sopko G. Hypoestrogenemia of hypothalamic origin and coronary artery disease in premenopausal women: a report from the NHLBI-sponsored WISE study. J Am Coll Cardiol. 2003;41:413–9. [PubMed: 12575968]
10. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Després J-P, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jiménez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW and Turner MB. Heart Disease and Stroke Statistics,2016 Update. A Report From the American Heart Association. 2015.
11. Kaplan JR and Manuck SB. Ovarian dysfunction and the premenopausal origins of coronary heart disease. Menopause. 2008;15:768–76. [PubMed: 18709705]
12. Adams MR, Kaplan JR and Koritnik DR. Psychosocial influences on ovarian endocrine and ovulatory function in Macaca fascicularis. Physiol Behav. 1985;35:935–40. [PubMed: 4095185]
13. Kaplan JR, Manuck SB, Anthony MS and Clarkson TB. Premenopausal social status and hormone exposure predict postmenopausal atherosclerosis in female monkeys. Obstet Gynecol. 2002;99:381–8. [PubMed: 11864663]

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14. Solomon CG, Hu FB, Dunaif A, Rich-Edwards JE, Stampfer MJ, Willett WC, Speizer FE and Manson JE. Menstrual Cycle Irregularity and Risk for Future Cardiovascular Disease. J Clin Endocrinol Metab. 2002;87:2013–2017. [PubMed: 11994334]
15. Punnonen R, Jokela H, Aine R, Teisala K, Salomaki A and Uppa H. Impaired ovarian function and risk factors for atherosclerosis in premenopausal women. Maturitas. 1997;27:231–8. [PubMed: 9288695]
16. Joakimsen O, Bonaa KH, Stensland-Bugge E and Jacobsen BK. Population-based study of age at menopause and ultrasound assessed carotid atherosclerosis: The Tromso Study. J Clin Epidemiol. 2000;53:525–30. [PubMed: 10812326]
17. Mack WJ, Slater CC, Xiang M, Shoupe D, Lobo RA and Hodis HN. Elevated subclinical atherosclerosis associated with oophorectomy is related to time since menopause rather than type of menopause. Fertil Steril. 2004;82:391–7. [PubMed: 15302289]
18. Dwyer KM, Nordstrom CK, Bairey Merz CN and Dwyer JH. Carotid Wall Thickness and Years Since Bilateral Oophorectomy: The Los Angeles Atherosclerosis Study. Am J Epidemiol. 2002;156:438–444. [PubMed: 12196313]
19. Parker WH, Broder MS, Chang EP, Feskanich, Farquhar C, Liu ZP, Shoupe D, Berek JS, Hankinson SS and Manson JE. Ovarian Conservation at the Time of Hysterectomy and Long-Term Health Outcomes in the Nurses' Health Study. [Article].
20. Martin BJ and Anderson TJ. Risk prediction in cardiovascular disease: the prognostic significance of endothelial dysfunction. Can J Cardiol. 2009;25 Suppl A:15A–20A.
21. Swerdlow AJ, Hermon C, Jacobs PA, Alberman E, Beral V, Daker M, Fordyce A and Youings S. Mortality and cancer incidence in persons with numerical sex chromosome abnormalities: a cohort study. Ann Hum Genet. 2001;65:177–88. [PubMed: 11427177]
22. Ostberg JE, Donald AE, Halcox JP, Storry C, McCarthy C and Conway GS. Vasculopathy in Turner syndrome: arterial dilatation and intimal thickening without endothelial dysfunction. J Clin Endocrinol Metab. 2005;90:5161–6. [PubMed: 15985480]
23. Noel Bairey Merz C, Johnson BD, Sharaf BL, Bittner V, Berga SL, Braunstein GD, Hodgson TK, Matthews KA, Pepine CJ, Reis SE, Reichek N, Rogers WJ, Pohost GM, Kelsey SF and Sopko G. Hypoestrogenemia of hypothalamic origin and coronary artery disease in premenopausal women: a report from the NHLBI-sponsored WISE study. Journal of the American College of Cardiology. 2003;41:413–419. [PubMed: 12575968]
24. Meczekalski B, Podfigurna-Stopa A and Genazzani AR. Hypoestrogenism in young women and its influence on bone mass density. Gynecological Endocrinology. 2010;26:652–657. [PubMed: 20504098]
25. Weitzmann MN and Pacifici R. Estrogen deficiency and bone loss: an inflammatory tale. The Journal of clinical investigation. 2006;116:1186–1194. [PubMed: 16670759]
26. Postnov A, Vinogradov A, Van Dyck D, Saveliev S and De Clerck N. Quantitative analysis of bone mineral content by X-ray microtomography. Physiological measurement. 2003;24:165. [PubMed: 12636194]
27. Nelson ME, Fisher E, Catsos P, Meredith C, Turksoy R and Evans W. Diet and bone status in amenorrheic runners. The American journal of clinical nutrition. 1986;43:910–916. [PubMed: 3717065]
28. Drinkwater BL, Nilson K, Chesnut CHI, Bremner WJ, Shainholtz S and Southworth MB. Bone Mineral Content of Amenorrheic and Eumenorrheic Athletes. New England Journal of Medicine. 1984;311:277–281. [PubMed: 6738640]
29. BILLER BM, COUGHLIN JF, SAXE V, SCHOENFELD D, SPRATT DI and KLIBANSKI A. Osteopenia in women with hypothalamic amenorrhea: a prospective study. Obstetrics & Gynecology. 1991;78:996–1001. [PubMed: 1945230]
30. Podfigurna-Stopa A, Pludowski P, Jaworski M, Lorenc R, Genazzani AR and Meczekalski B. Skeletal status and body composition in young women with functional hypothalamic amenorrhea. Gynecological Endocrinology. 2012;28:299–304. [PubMed: 21957879]
31. Pauli SA and Berga SL. Athletic amenorrhea: energy deficit or psychogenic challenge? Annals of the New York Academy of Sciences. 2010;1205:33–38. [PubMed: 20840250]

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32. Brundu B, Loucks TL, Adler LJ, Cameron JL and Berga SL. Increased cortisol in the cerebrospinal fluid of women with functional hypothalamic amenorrhea. The Journal of Clinical Endocrinology & Metabolism. 2006;91:1561–1565. [PubMed: 16464944]
33. Suh B, Liu JH, Berga S, Quigley M, Laughlin G and Yen S. Hypercortisolism in Patients With Functional Hypothalamic-Amenorrhea*. The Journal of Clinical Endocrinology & Metabolism. 1988;66:733–739. [PubMed: 3346352]
34. Grinspoon S, Miller K, Coyle C, Krempin J, Armstrong C, Pitts S, Herzog D and Klibanski A. Severity of Osteopenia in Estrogen-Deficient Women with Anorexia Nervosa and Hypothalamic Amenorrhea 1. The Journal of Clinical Endocrinology & Metabolism. 1999;84:2049–2055. [PubMed: 10372709]
35. Lawson EA, Donoho D, Miller KK, Misra M, Meenaghan E, Lydecker J, Wexler T, Herzog DB and Klibanski A. Hypercortisolemia is associated with severity of bone loss and depression in hypothalamic amenorrhea and anorexia nervosa. The Journal of Clinical Endocrinology & Metabolism. 2009;94:4710–4716. [PubMed: 19837921]
36. Hahn TJ, Halstead LR, Teitelbaum SL and Hahn B. Altered mineral metabolism in glucocorticoid-induced osteopenia. Effect of 25-hydroxyvitamin D administration. Journal of Clinical Investigation. 1979;64:655. [PubMed: 457875]
37. Galliford T, Murphy E, Williams A, Bassett J and Williams G. Effects of thyroid status on bone metabolism: a primary role for thyroid stimulating hormone or thyroid hormone? Minerva endocrinologica. 2005;30:237–246. [PubMed: 16319811]
38. Tuchendler D and Bolanowski M. The influence of thyroid dysfunction on bone metabolism. Thyroid research. 2014;7:1. [PubMed: 24484647]
39. Torstveit MK and Sundgot-Borgen J. The female athlete triad: are elite athletes at increased risk? Medicine & Science in Sports & Exercise. 2005;37:184–193. [PubMed: 15692312]
40. Marcus MD, Loucks TL and Berga SL. Psychological correlates of functional hypothalamic amenorrhea. Fertility and sterility. 2001;76:310–316. [PubMed: 11476778]
41. Giles DE and Berga SL. Cognitive and psychiatric correlates of functional hypothalamic amenorrhea: a controlled comparison. Fertility and sterility. 1993;60:486–492. [PubMed: 8375531]
42. Laughlin G, Dominguez C and Yen S. Nutritional and Endocrine-Metabolic Aberrations in Women with Functional Hypothalamic Amenorrhea 1. The Journal of Clinical Endocrinology & Metabolism. 1998;83:25–32. [PubMed: 9435412]
43. Verri A, Nappi RE, Cecchini AP, Vallero E, Luzi S and Zara C. Eating disorders and Axis I psychiatric comorbidity in amenorrheic women. International Journal of Eating Disorders. 1998;24:137–146. [PubMed: 9697012]
44. Ahmed B, Merz CNB, Johnson BD, Bittner V, Berga SL, Braunstein GD, Hodgson TK, Smith K, Shaw L and Kelsey SF. Diabetes mellitus, hypothalamic hypoestrogenemia, and coronary artery disease in premenopausal women (from the National Heart, Lung, and Blood Institute sponsored WISE study). The American journal of cardiology. 2008;102:150–154. [PubMed: 18602512]
45. McEwen BS, Akama KT, Spencer-Segal JL, Milner TA and Waters EM. Estrogen effects on the brain: actions beyond the hypothalamus via novel mechanisms. Behavioral neuroscience. 2012;126:4. [PubMed: 22289042]
46. Ruhé HG, Mason NS and Schene AH. Mood is indirectly related to serotonin, norepinephrine and dopamine levels in humans: a meta-analysis of monoamine depletion studies. Molecular psychiatry. 2007;12:331–359. [PubMed: 17389902]
47. Amin Z, Canli T and Epperson CN. Effect of estrogen-serotonin interactions on mood and cognition. Behavioral and cognitive neuroscience reviews. 2005;4:43–58. [PubMed: 15886402]
48. Groothuis P, Dassen H, Romano A and Punyadeera C. Estrogen and the endometrium: lessons learned from gene expression profiling in rodents and human. Human reproduction update. 2007;13:405–417. [PubMed: 17584823]
49. Samsioe B Urogenital aging—a hidden problem. American journal of obstetrics and gynecology. 1998;178:S245–S249. [PubMed: 9609599]
50. Bachmann GA and Nevadunsky NS. Diagnosis and treatment of atrophic vaginitis. American family physician. 2000;61:3090–3096. [PubMed: 10839558]

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51. Veleva Z, Tiitinen A, Vilska S, Hydén-Granskog C, Tomás C, Martikainen H and Tapanainen JS. High and low BMI increase the risk of miscarriage after IVF/ICSI and FET. Human reproduction. 2008;23:878–884. [PubMed: 18281684]
52. Schleußner E The prevention, diagnosis and treatment of premature labor. Dtsch Arztebl Int. 2013;110:227–36. [PubMed: 23596503]
53. Maconochie N, Doyle P, Prior S and Simmons R. Risk factors for first trimester miscarriage—results from a UK-population-based case–control study. BJOG: An International Journal of Obstetrics & Gynaecology. 2007;114:170–186. [PubMed: 17305901]
54. Rondo P, Ferreira R, Nogueira F, Ribeiro M, Lobert H and Artes R. Maternal psychological stress and distress as predictors of low birth weight, prematurity and intrauterine growth retardation. European journal of clinical nutrition. 2003;57:266–272. [PubMed: 12571658]
55. Berga SL, Marcus MD, Loucks TL, Hlastala S, Ringham R and Krohn MA. Recovery of ovarian activity in women with functional hypothalamic amenorrhea who were treated with cognitive behavior therapy. Fertility and sterility. 2003;80:976–981. [PubMed: 14556820]
56. Michopoulos V, Mancini F, Loucks TL and Berga SL. Neuroendocrine recovery initiated by cognitive behavioral therapy in women with functional hypothalamic amenorrhea: a randomized, controlled trial. Fertility and sterility. 2013;99:2084–2091. e1. [PubMed: 23507474]
57. Bagnasco M, Dube M, Kalra P and Kalra S. Evidence for the existence of distinct central appetite, energy expenditure, and ghrelin stimulation pathways as revealed by hypothalamic site-specific leptin gene therapy. Endocrinology. 2002;143:4409–4421. [PubMed: 12399438]
58. Warren M, Voussoughian F, Geer E, Hyle E, Adberg C and Ramos R. Functional hypothalamic amenorrhea: hypoleptinemia and disordered eating. The Journal of Clinical Endocrinology & Metabolism. 1999;84:873–877. [PubMed: 10084564]
59. Welt CK, Chan JL, Bullen J, Murphy R, Smith P, DePaoli AM, Karalis A and Mantzoros CS. Recombinant human leptin in women with hypothalamic amenorrhea. New England Journal of Medicine. 2004;351:987–997. [PubMed: 15342807]
60. Schenker JG, Yarkoni S and Granat M. Multiple pregnancies following induction of ovulation. Fertility and sterility. 1981;35:105. [PubMed: 7009218]
61. Hurley DM, Brian RJ and Burger HG. Ovulation induction with subcutaneous pulsatile gonadotropin-releasing hormone: singleton pregnancies in patients with previous multiple pregnancies after gonadotropin therapy. Fertility and sterility. 1983;40:575–579. [PubMed: 6354756]
62. Jayasena CN, Nijher GM, Chaudhri OB, Murphy KG, Ranger A, Lim A, Patel D, Mehta A, Todd C and Ramachandran R. Subcutaneous injection of kisspeptin-54 acutely stimulates gonadotropin secretion in women with hypothalamic amenorrhea, but chronic administration causes tachyphylaxis. The Journal of Clinical Endocrinology & Metabolism. 2009;94:4315–4323. [PubMed: 19820030]
63. Ruman J, Luna M, Messenger C and Copperman A. Women with hypothalamic amenorrhea undergoing in vitro fertilization have a favorable prognosis despite higher stimulation requirements. Fertility and Sterility. 2008;90:S236–S237. [PubMed: 19007637]
64. Cobb KL, Bachrach LK, Sowers M, Nieves J, Greendale GA, Kent KK, Brown BW, Pettit K, Harper DM and Kelsey JL. The effect of oral contraceptives on bone mass and stress fractures in female runners. Medicine and science in sports and exercise. 2007;39:1464. [PubMed: 17805075]