

Effect of Exercise on Reproductive Hormones in Female Athletes

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Abstract

Female athlete who engages in high intensity exercise is at risk as a consequence of hormonal changes which result in menstrual disturbances. Impaired production of gonadotrophins, which leads to luteal phase deficiency and anovulation, is a common hormonal finding with exercise-induced menstrual disturbances. There is a strong agreement in responsibility of low energy availability due to imbalance between energy intake and energy expenditure during exercise to impairment hypothalamus ovarian axis (HPO) and reduction in hypothalamus, gonadotropin hormones and subsequently menstrual disorder. However, increase in stress hormone levels through hypothalamus adrenal axis (HPA) activated by strenuous physical activity has been introduced as a responsible for HPO axis impairment by some other studies. This paper summarized the effect of prolonged or high-intensity exercise in female reproductive hormone and cycle in female athletes and animal models.

Keywords: Exercise, Female Reproductive Hormone, Female Athlete Triad

Introduction

Regular and healthy reproductive cycle (eumenorrhoea) is a complex process comprising the coordinated interaction of neurotransmitter systems, hypothalamic releasing factors, anterior pituitary gland hormones, gonadal sex steroid hormones, and various growth factors. Ovarian hormones such as estrogen and progesterone are main hormones for female reproductive and menstrual cycle. The ovarian cycle is stimulated by hormones in the circulation, i.e. follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which are, in turn, regulated by the hypothalamic gonadotropin releasing hormone (GnRH). GnRH released by hypothalamus stimulates anterior pituitary gland to release LH and FSH. These hormones enhance ova, i.e. egg development in ovaries [1, 2].

Duration of normal reproductive cycle in female is about 26-35 days and divided into two phases, i.e. follicular phase and luteal phase. The follicular phase is characterized by high concentration of FSH and gradually increase in estrogen level which mainly secreted by the ovaries, whilst the luteal phase is characterized by high concentrations of LH and increase in estrogen and progesterone secretion by corpus luteum [1, 2]. Estrogen and progesterone secreted by ovaries prepare uterus

for pregnancy. Following ovum maturation, anterior pituitary is stimulated by rising estrogen level to release more LH and FSH. Estrogen level drops, prior to ovulation while FSH and LH levels reach to peak to cause the release of mature ovum into fallopian tube. The residue cell of the ruptured follicle begins to secrete progesterone and some estrogen to trigger thickening uterine lining and prepare the endometrium for pregnancy. In the absence of pregnancy, menstruation or vaginal bleeding occurs, about 8 days after ovulation which is followed by low estrogen and progesterone levels as well as endometrium deterioration. Estrogen plays an important role in many parts of the body such as adipose tissue, skin, and bone tissue. Estrogen also promotes development and maintenance of female reproductive structure and female secondary sex characteristics. Progesterone acts with estrogen to prepare endometrium for implantation and inhibits the release of GnRH and LH [3].

EXERCISE AND FEMALE REPRODUCTIVE HORMONES

In recent years, young women have become increasingly active in sport events. Even though physical activity and exercise provide substantial health benefits, reproductive disorders and subsequent osteoporosis have been still increased in the female population of participating in strenuous sport activities. Female athlete triad is defined as a syndrome to describe the spectrum of disorders related to energy availability, menstrual function and bone mineral density in female athletes.

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It is recognized as a healthy problem which may decrease physical performance and even cause morbidity and/or mortality [4, 5, 6, 7]. Clinical symptoms of the female athlete triad include eating disorder, functional hypothalamic amenorrhea and osteoporosis [8].

Other signs include anemia, depression, fatigue, cold intolerance and destroyed tooth enamel by frequent vomiting [9]. High intensity training, low energy availability, low leptin level, low body weight or low body fat and stress hormones produced by psychological stress may lead to altering the endocrine pathway and menstrual cycle [1, 7, 10]. Disturbance of GnRH pulsatility due to hypothalamic dysfunction following exhausting exercise may result in delayed menarche and disruption of menstrual cyclicity [11]. It is undoubted that exercise is beneficial to help the preservation of bone health and prevention of osteoporosis during puberty and growth. However, excessive exercise may also lead to primary amenorrhea and low bone mineral density (BMD) during puberty and lead to secondary amenorrhea and bone loss after puberty [12].

It was reported that prolonged running suppressed pulsatile secretion of serum LH level in rats [13-15]. Moreover, exercise training was accompanied with increased serum cortisol concentration and decreased LH concentration with normal FSH concentration in mares [16, 17]. However, it was reported by Bullen et al. [18] that an 8-week moderate endurance exercise did not affect LH level and this finding was similar to another study which reported that LH concentration did not change after bicycle ergometer exercise in middle-distance runners [19]. Whereas, some studies reported that restricted energy availability following intense exercise caused the reduction in LH concentration via disruption of GnRH release in females [1, 20-22].

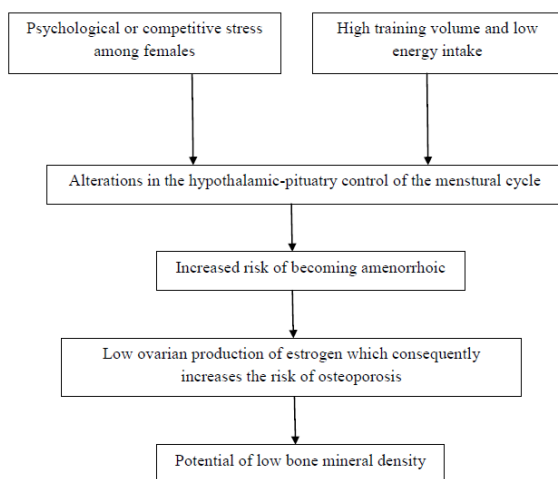


Figure.1 The spectrum of the female athlete triad. Adapted from Birch, K. (2005) [1].

PATHOPHYSIOLOGY OF REPRODUCTIVE DYSFUNCTION IN FEMALE ATHLETES

Energy availability which is described as dietary energy

intake minus exercise energy expenditure may play a critical role in female reproductive health [20, 23]. Hormonal disorders may be occurred while the energy availability below 30 kcal per kg of lean tissue or fat free mass. Low energy availability and chronic energy deficiency causing disruption in the HPO axis are assumed to be the primary and important causal factors in the hypoestrogenism observed in female athletes who participate in particular sports such as ballet dancing, long distance running, gymnastics and figure skating [6, 11, 20, 24].

Low energy availability causes reduction in circulating levels of insulin and insulin-like growth factor I (IGF-I) which is accompanied by elevated levels of IGF-binding protein-1 and cortisol. This reduction in IGF-I activity debilitates stimulation of the hypothalamic-pituitary-gonadal (HPG) axis, while the increased cortisol inhibits hypothalamic secretion of GnRH [25]. Suppression of hypothalamic pulsatile release of GnRH inhibits the secretion of LH and FSH from pituitary gland which in turn diminishes ovarian stimulation and estradiol production. Prolonged follicular phase due to the absence of LH or the estradiol surge in mid-cycle, results in menstrual cycles disorder. Delayed menarche or primary and secondary amenorrhea are resulting from very low LH level [21, 26-29]. Leptin hormone, which is a protein produced by the obesity gene and secreted by the adipocyte, may be a critical factor engaged in signaling low energy availability to the HPO axis [11]. Additionally, stress induced by excessive exercise that activates the HPA axis may play an inhibitory role on HPO axis. GnRH released from hypothalamus is inhibited by corticotropin-releasing hormone (CRH) resulting in the suppression of LH and ovarian estrogen and progesterone release [11, 30]. Since, estrogen plays a great role in the maintenance of bone mineral density (BMD), hypo-estrogenic status was suggested to associate low BMD and increased risk of osteoporosis [1]. The pathophysiology of reproductive dysfunction among female athletes is presented in Figure 1.

A study done by Hagmar et al. [31] showed that female athletes who participated in different Olympic sports events had an anabolic effect in body composition and the biomarkers of energy availability were within normal range. It was also observed that most of the menstrual disorders in female athletes are due to polycystic ovarian syndrome (PCOS). The most endocrinological reason of menstrual disturbance was due to hyper-androgenic condition of PCOS, rather than the hypothalamic inhibition due to low energy availability. In the female athletes with PCOS, LH/FSH ratio and androgen levels were higher than those who had regular menstruation.

Study done by Bullen et al. [18] on 7 young women showed that moderate bicycle ergometer training in fixed relative intensity exhibited increase in beta endorphin, beta lipotropin and cortisol, and reproductive hormone levels. Cyclic menstruation and preovulatory gonadotropin surges continued in all subjects. However, some of the subjects showed a reduction in the levels of estradiol and free progesterone, with subsequent disturbance in ovarian function. The acceleration rate and exercise intensity have influences on menstrual cycle. Menstrual function was more affected by long term exercise at the level of energy expenditure above the lactate threshold than

long-term exercise with below the lactate threshold. It was reported that progressive, moderate intensity exercise program in female distance runners does not affect reproductive system in matured eumenorrheic women [32].

In 2001, an investigation was done by Williams et al. [33] in which sixteen adult female cynomolgus monkeys following the gradual training regimen were encouraged to run on the treadmill. Suppression of GnRH secretion followed by lengthening of follicular phase and a decline in progesterone synthesized by corpus luteum leading to amenorrhea were observed. Another study by Williams et al. [34] on eight adult female cynomolgus monkeys with training program which

consisted of treadmill running 7 days per week at 2 hours per day for 7 to 24 months provided strong support to suggest that exercise induced menstrual disturbance. These menstrual disturbances were suggested to be the results of low energy availability produced by the increased energy expenditure due to vigorous and regular exercise regimen. Nevertheless, changes in body weight are not necessarily related to the development of reproductive disorder caused by low energy availability. However, the induction and reversal of amenorrhea was intimately related to energy availability in an exercise training female cynomolgus model.

Table.1 Summarizes some selected studies on the effects of different mode and intensity of exercise on female reproductive cycle in animal and human studies

Type of study	Studies	Population	Exercise training program	Key findings
Animals	Blake et al, 1984 [13]	Female Wistar rats	8 weeks of daily treadmill running	Fatiguing resulted in reduction in serum luteinizing hormone levels and increase in beta-endorphin and leucine enkephalin (LE). Trained-fatigued animals exhibited less LE in the amygdala than the trained-nonfatigued rats. These findings indicated an acute, fatigue-running modulation of the hypothalamic-pituitary-gonadal axis
	Axelson et al, 1987 [36]	Female rats	Two mode of exercise: forced swimming and swimming plus running, were gradually increased in duration to a maximum of 2.5 hours for 8 weeks	Exercise decreased ovarian steroids levels, increased corticosterone levels, and disrupted vaginal cycles.
	Manning and Bronson, 1989 [14]	Immature female rats	Prolonged running wheel in order to obtain food	Prolonged exercise blocked the pulsatile release of LH
	Manning and Bronson, 1991 [15]	young female rats	Prolonged running wheel in order to obtain food	The pulsatile secretion of LH and growth hormone were completely suppressed. Mean levels of FSH, prolactin, and TSH were not affected. Prolonged exercise elevated corticosterone titers, and the secretory pattern of this steroid was changed out of phase with running activity
	Westerlind et al, 2002 [37]	Female Sprague-Dawley rats	Moderate exercise training : Treadmill training 20–25 m min ⁻¹ , 15% grade, 30 min/day, 5 days/ week	no significant changes in steroid hormones such as progesterone and estradiol
	Williams et al, 2001a [33]	Adult female cynomolgus monkeys	Treadmill training at 12 km per day, 7 days / week, 2 h/ day, with a 3-min break after each 30-min running period	Significant declines in plasma reproductive hormone concentrations, an increase in follicular phase length, and a decrease in luteal phase progesterone secretion
	Williams et al, 2001b [34]	Adult female cynomolgus monkeys	Treadmill running 7 days per week at 2 hours per day is for 7 to 24 months	Monkeys developed amenorrhea with low and unchanged concentrations of LH, FSH, E2) after gradually increasing their daily exercise to 12.3 ± 0.9 km/day of running over a 7 to 24 month period
	Kelley et al, 2009 [16]	Horse mare, ages 3 to 15	6 days /week for 30 min; 10 min trot (4.0 m/s), 5 min canter (5.2 m/s), 5 min trot (4.0 m/s), 5 min canter (5.2 m/s), 5 min trot (4.0 m/s)	Maximum LH concentrations were lower and mean cortisol concentrations were increased and no differences were found in FSH concentration
	Dos Santos	Female Wistar rats	Physical training on a motor	Physical training alone was not responsible

	et al, 2011 [35]		treadmill with a gradual increase in speed and time	for significant changes in reproductive function. Combination of food restriction and exercise was able to interrupting the estrous cyclicity in all animals. Leptin appears to be one among others factors related to estrous cycle, and had indirect affect on estrous cycle
	Kelley et al, 2011 [17]	Light-horse mares aged 3 to 15 year	Moderate exercise for 30 min, 6 day/week	Moderately exercise induced higher cortisol concentrations, lower peak LH concentrations, and altered ovarian follicular dynamics
	Mosavat et al, 2012 [38]	Female rats	80 and 20 jumps per day for 8 weeks	Lower level of LH concentration in 80 jumps /day group
Athlete	Veldhuis et al, 1985 [39]	Woman distance runners	Distance runners	6 of 9 amenorrheic distance runners had a reduction in spontaneous LH pulse frequency. This reduction in LH pulse frequency happened without any significant alterations in plasma concentrations of estradiol and free testosterone or 24h integrated serum concentrations of LH, FSH, or prolactin
	Thong et al, 2000 [40]	Female athletes	Running and cycling at maximal aerobic capacity (VO ₂ max) determined by a running protocol was required to be above 55 and 48 ml·min ⁻¹ ·kg ⁻¹	Leptin was significantly lower in amenorrheic athletes. Hypoleptinemia in EAA was corresponding by reductions in caloric intake, estradiol, insulin, and thyroid hormones
	Rahnama et al, 2004 [19]	Female middle-distance runners, age 22.8 ± 2.2 years	Athletic females had an average of 3.5 ± 0.5 years experience in competitive running at 800 and 1500 meters (3 sessions training / week)	No significant difference was found between the athletic and nonathletic women in progesterone, LH and FSH concentration
	Hagmar et al, 2009 [31]	Swedish female Olympic athletes	Investigate the menstrual status, body composition, and biomarkers of energy availability and clarify the endocrine mechanisms underlying menstrual disturbances in female Olympic athletes participating in power, endurance, and technical sport disciplines	Menstrual dysfunction was 27% and associated with polycystic ovary syndrome (PCOS) and not hypothalamic inhibition because of energy deficiency
Non-athlete	Bullen et al, 1984 [41]	Young women	8-week training of 'sixty-min' continuous bicycle in moderate intensity	Ovarian function was disturbed in 4 subjects as evidenced by decreased excretion of estriol, free progesterone, or both
	Bullen et al, 1985 [42]	Untrained college women	Run 4 miles (6.4 km) /day, progressing to 10 miles (16.1 km)/ day by the 5 week, and to engage daily in 31/2h of moderate-intensity sports	vigorous exercise, particularly compounded by weight loss, can reversibly disturb reproductive function in women
	Rogol et al, 1992 [32]	Healthy eumenorrheic (age 17.8 +/- 0.9 year) untrained women	undertook a 1-year training program at one of two exercise intensities, subjects ran approximately 790 miles	No significant changes for any parameter of pulsatile LH release and nutritional intake
	Loucks et al, 1998 [20]	Healthy eumenorrheic and untrained women 18 to 29 year old	Prolonged treadmill running	Low energy availability reduced LH pulse frequency by 10% during the waking hours and increased LH pulse amplitude by 36%. These results have shown that that LH pulsatility is depend on energy availability not exercise stress
	Loucks and Thuma, 2003 [21]	Untrained young women	Subjects expended 15 kcal/kg of lean body mass (LBM)/ day in managed exercise at 70% of aerobic capacity	LH pulsatility was unaffected by an energy availability of 30kcal/kg LBM·d, and below this threshold LH pulse frequency decreased, whereas LH pulse amplitude

				increased. This disruption was more great in women with short luteal phases
	Kossman et al, 2011 [43]	Eumenorrheic woman, age 25-35year	5 menstrual cycles of treadmill running with a 12 week progression to 300 min/week at 80–85% of Vo2max	Estrogen declined by 18.9% and progesterone by 23.7%. These reductions were due to decreased luteal phase levels. However, menstrual cycle and luteal phase lengths were unchanged
	Smith et al, 2011 [44]	Untrained, healthy, young eumenorrheic women	30 minutes of aerobic exercise 5 times/ week for duration of 16 weeks	No significant changes menstrual cycle length. Significant reduction in progesterone level and no so significant changes in other sex hormones

Kelley et al. [17] evaluated the effects of exercise on ovarian folliculogenesis and related hormones in mares, which showed that moderate exercise significantly stimulated stress response in mares and decreased LH levels. The interovulatory interval was increased and follicular dynamics were changed. Cortisol concentrations in horses were increased depending on various exercise duration and intensity. Long duration exercise induced higher cortisol levels than shorter with intense exercise. It was suggested that the suppression of LH concentration was due to an increase in cortisol level and the lengthened interovulatory intervals were the consequence of exercise-induced stress in mares. Dos Santos et al. [35] reported that intensive exercise without food restriction was not able to cause significant changes in estrous cycle and estradiol level. Although food restriction was capable to decrease leptin level in some of rats, the combination of exercise and food restriction were responsible for interruption in estrous cycle in all rats. The effects of exercise intensity and its duration on female reproductive hormones in animals, female athletes and untrained women are summarized in Table1.

Conclusion

It has been indicated that exercise, specially prolonged and high intensity has an adverse effect on female reproductive hormones. Low energy availability, low leptin level and high stress hormone concentration following prolonged or strenuous exercise interrupt HPO axis and releases of female reproductive hormones. This interruption may lead to abnormal menstrual cycle associated with luteal phase deficiency and anovulation. It is needed to further investigate the possible interventions which may be beneficial to reduce or prevent the impacts on reproductive health among female athletes following prolonged and high intensity exercise.

Abbreviations

FSH: Follicle stimulating hormone, LH: Luteinizing hormone, BMD: Bone mineral density, HPO axis: Hypothalamus pituitary ovarian axis, HPA axis: Hypothalamus pituitary adrenal axis, HPG axis: Hypothalamus pituitary gonadal axis, CRH: corticotropin releasing hormone, PCOS: polycystic ovarian syndrome, IGF-I,

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