Energy balance and reproductive function

Regulation of reproductive function in athletic women: an investigation of the roles of energy availability and body composition

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Exercise associated reproductive dysfunction in women is attributable to deficits of readily available energy

Reproductive dysfunction is common in female athletes and is indicated symptomatically by delayed menarche (primary amenorrhoea) in girls, and by a cessation of menses (secondary amenorrhoea) or sporadic menses (oligomenorrhoea) in adolescents and young women. These menstrual disturbances reflect different degrees of ovarian suppression and are accompanied by inadequate follicular development and impaired fertility. Exercise associated ovarian suppression coincides with a multitude of metabolic and physiological disturbances that can impact deleteriously on health. Of particular prominence is a disruption of bone metabolism, which reduces bone acquisition during adolescence and elicits premature bone loss in adulthood.[1]

The mechanism of exercise associated ovarian suppression is neuroendocrine dysfunction.[2] The accompanying menstrual disturbance is termed functional hypothalamic amenorrhoea (FHA), which denotes its origin and attributes its aetiology to a reversible adaptation to physiological or emotional stress. In FHA, there is disruption of the pulsatile release of gonadotropin releasing hormone (GnRH) from the arcuate nucleus of the hypothalamus, which alters the pulsatile release of the pituitary gonadotropin, luteinising hormone (LH). The consequence is diminished ovarian stimulation.[2] At present, the precise cause of this neuroendocrine dysfunction is equivocal. A number of aetiological factors have been implicated, which tend to coincide in affected athletes, and include physical training itself, weight loss or the maintenance of a reduced body fat content, and low cellular energy (or specifically glucose) availability.[3] Energy availability is assessed practically as dietary energy intake minus exercise energy expenditure.[3]

Fundamental insight into the aetiology of exercise associated ovarian suppression has emerged from observations of the prevalence of the disorder among different cohorts of athletes, in conjunction with their physical, nutritional, and training characteristics. Athletes with FHA have been observed to practice sports for which a slender physique confers an aesthetic or performance related advantage. They typically train intensely, eat sparingly and are underweight and exceptionally lean.[1] Such athletes have been compared with anorexic women because of certain similarities in their physique, physiology, metabolism, and personality.[1] Both groups of women exhibit FHA and display a distinctive metabolic profile, which reduces basal metabolic rate, retards protein turnover, and is therefore counter-regulatory to energy deprivation.

> ''An abrupt, short term increase in physical activity in previously sedentary women with normal ovarian function only disrupts LH pulsatility if dietary energy intake is insufficient to achieve an energy balance''

The culmination of chronic or repeated cycles of low energy availability is weight loss, which when sustained, results in reduced body fat content. Current perception is that low energy availability and lack of body fat are both fundamental triggers for disruption of the hypothalamic GnRH pulse generator and that the presence of both factors leads to a greater degree of ovarian suppression. An abrupt, short term increase in physical activity in previously sedentary women with normal ovarian function only disrupts LH pulsatility if dietary energy intake is insufficient to achieve an energy balance.[3] Furthermore, in cynomolgus monkeys, exercise associated FHA is reversible with increased energy intake, despite the maintenance of continued training.[4] Interestingly, the development and reversal of FHA in these monkeys is closely correlated with changes in the plasma concentration of 3,5,3′-triiodothyronine, a marker of energy availability and metabolic rate. Because the susceptibility to exercise associated FHA is greater in leaner women,[1 2] it is likely that low energy availability and a low body fat content interact to disrupt LH pulsatility. On the basis of this theory, there must be one or a number of metabolic signals that inform the hypothalamus of these nutritional deficits.

Over the past 10 years, there has been accumulating evidence to support a leading role for the hormone leptin as a metabolic signal to the hypothalamus of energy availability and the magnitude of energy stores. Leptin is a cytokine-like protein encoded by the *ob* gene and expressed within white adipose tissue.[5] Its rate of secretion and plasma concentration reflect fat mass and plasma insulin concentration. Consequently fat loss, which increases insulin sensitivity and reduces plasma insulin concentration, elicits a decline in plasma leptin concentration. However, even short term energy deficit before significant changes in adiposity reduces plasma leptin concentration in conjunction with falls in the plasma concentrations of insulin and triiodothyronine.[5] Lean women with exercise associated FHA have low plasma triiodothyronine concentration, unusually high insulin sensitivity, and low plasma leptin concentrations that fail to fluctuate distinctively with meal ingestion.[6 7] In anorexic women, refeeding and gains in fat mass coincide with increases in the plasma concentrations of leptin, insulin, and triiodothyronine.[8]

> ''the reversal of hypogonadism in these energy deficient women treated with leptin was accompanied by a reversal of other metabolic disturbances in the absence of weight gain''

Perhaps the most convincing evidence to date of a critical role for leptin as a signal to the hypothalamus of energy deprivation in women with exercise/diet associated FHA is provided by a recent study which showed that treatment of such women with recombinant human leptin restored ovulatory menstrual cycles.[9] Furthermore, the reversal of hypogonadism in these energy deficient women treated with leptin was accompanied by a reversal of other metabolic disturbances in the absence of weight gain. Of interest, another recent study has shown that active, underweight women with behavioural characteristics of anorexia nervosa, who curiously remain eumenorrhoeic, differ from their amenorrhoeic counterparts by the presence of a higher body fat content and plasma leptin concentration.[10]

In conclusion, current research evidence suggests that exercise associated reproductive dysfunction in women is nutritional in origin and may be attributed to a deficit of readily available energy, primarily in the form of circulating glucose, liver glycogen, and adipose tissue triacylglycerol. A low plasma insulin concentration, consequent to a low blood glucose concentration, a low body fat content, or both of these factors, is accompanied by a disturbance of leptin secretion and a reduced plasma leptin concentration. It would seem that a reduction in plasma leptin concentration below a critical threshold value, for a significant period of time, disturbs the activity of the hypothalamic GnRH pulse generator, which instigates the endocrine events that lead to ovarian stimulation. The susceptibility to ovarian suppression and FHA is therefore greatest in lean women with chronically low energy availability, as indicated by a reduced plasma triiodothyronine concentration. To avoid reproductive dysfunction, female athletes should consume adequate energy and carbohydrate to balance energy expenditure and replace glycogen. They should avoid abrupt and rapid weight loss and maintain an "adequate" body fat content, which may be individually specific, but coincides with regular menses.

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COMMENTARY

The reproductive system is extremely sensitive to nutritional restriction. One model of nutritional restriction is the thin exercising athlete who may have low body fat reserves and exercises intensely, causing an energy output that is beyond her nutritional intake. Recent work on the neuropeptides that regulate food intake and metabolism has revealed that a peripheral signal from the fat cell in the form of the hormone leptin transmits a signal to the hypothalamus, which enables the body to determine nutritional status. In addition, leptin is sensitive to energy deficient states, indicating that it also acts as a short term metabolic signal. Interestingly, leptin expression in the fat cells depends on glucose oxidation, indicating dependence on metabolic fuels. Thus food is necessary for leptin synthesis, and fat cells are necessary as a site of production. Inadequate leptin leads to shutdown of the reproductive system. The production of this hormone appears to be compromised in the athlete who is exercising intensely and has low body fat. In her paper Dr Zanker reviews our understanding of the process, which when left unchecked can lead to bone loss. The administration of leptin in hypothalamic amenorrhoea can reverse the amenorrhoea in some people, but the effect on bone is unknown. There is much interest in bone loss at present, which appears to have a nutritional basis with possibly a hormonal component in the form of hypo-oestrogenism. However, the administration of oestrogen has not uniformly led to a reversal of bone loss, whereas refeeding has a powerful anabolic effect with significant increases in bone mass. A number of enigmas remain. Although for most athletes there is a return of menstrual function with an increase in energy intake, a decrease in exercise, or an increase in body fat, some do not have a reversal. The restraining mechanisms in this situation are as yet unknown.

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Female athlete triad

The myth of the female athlete triad

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The female athlete triad is defined as a syndrome consisting of three necessary components: (*a*) disordered eating; (*b*) amenorrhoea; (*c*) osteoporosis.[1] The American College of Sports Medicine (ACSM) published a Position Stand in 1997,[1] and at that time indicated a strong need for more epidemiological, laboratory, and clinical data to support the importance of this syndrome. Currently, the prevalence of regular vigorous activity among adolescent girls remains out of reach of the Year 2010 objectives,[2] and the problem of overweight among young people has achieved epidemic proportions in the United States and other industrialised countries.[3] Our concern is that triad related data may be misinterpreted and used as justification for setting health and social policies that may ultimately counter the US Public Health Service efforts to promote the benefits of athletic participation and an active lifestyle among children and adolescents.[4] Moreover, there are ample historical and medical examples of iatrogenic eating and psychosexual disorders ascribed to otherwise healthy, hard driving, and passionate women in their pursuit of social independence, political power, or athletic excellence.[5–8] In fact, until 1972, women were banned from very challenging athletic events such as the marathon, because officials of the Amateur Athletic Union (AAU) believed that such competition would be harmful to female reproductive function.[8] Therefore we maintain that, as girls and young women are currently striving to attain the same level of accessibility and achievement in organised sports as their male counterparts, the creation of yet another form of female specific pathology undermines this hard earned success and may have other serious implications for their health and well-being. Our purpose in writing this article is to describe the female athlete triad with regard to its epidemiology and physiology and to offer our comments and opinions which challenge many of