EXERCISE AND MENSTRUAL DYSFUNCTION

(Received 27 July, 1991)

M. Erenus, M.D.*

* *Assistant Professor, Department of Obstetrics and Gynecology, Faculty of Medicine, Marmara University, İstanbul, Turkey.*

SUMMARY

Moderate exercise is undoubtedly a positive factor in health. Strenuous exercise in women may lead to disturbances in reproductive function ranging from subtle effects on fertility to hypoestrogenic amenorrhea. Exercise-related menstrual dysfunction is more likely to occur with strenuous exercise, in women who are nulliparous, in women with a history of delayed menarche, in women under age 30, and in women with low body fat. The mechanism by which the menstrual dysfunction develops is, to this point, unknown, but no evidence exists to suggest that it has long-term repercussions on reproductive capacity.

INTRODUCTION

Awareness of the connection between health and physical fitness has led an increasing numbers of individuals, men and women, to under take regular physical exercise. There has been a corresponding explosion in the fitness industry, with a proliferation of fitness clubs and sales of sports clothing and equipment. In the last decade and a half, increasing numbers of women have begun participating in strenuous exercise, and it has become clear that there is an association between menstrual dysfunction and exercise. The pathophysiology responsible for the association, however, now known to include delayed menarche (1), luteal phase deficiency (2) and oligomenorrhea or amenorrhea (3), remains unknown, although most hypothesis invoke a role for endogenous opioid peptides. Similarly, it is unclear whether the reproductive dysfunction is a simple abnormality resulting from undue physical stress, or it represents an adaptive function to improve athletic performance.

Reproductive Disorders:

As described, the reproductive disorders associated with exercise form a spectrum ranging from marked (delay of puberty primary amenorrhea) to subtle (luteal deficiency) effects. These will be discussed in turn.

(1) Delay of menarche:

Competetive athletes and ballet dancers undergo pubertal development and menarche later than non-training peers. This has been established in a number of studies (4-6), but it remains controversial whether the delayed development is a result of physical stress, emotional stress, or delayed pubertal development produces social pressures which coerce young girls into particular athletic activities. Some authors maintain that certain activities fovour a particular physique which may itself predispose to delayed pubertal development (7,8); this is a tempting hypothesis with respect to gymnastics and ballet dancing.

Pubertal development in girls, undergoing exercise training is probably affected as much by exercise as by fixed and restricted eating patterns, which appear to develop in early adolescence. Girls in special groups (gymnastics, figure skaters and ballet dancers) follow restrictive diets to achieve the ideal physiognomy for their performance (9,10). The incidence of anorexia nervosa in these groups is much higher than in the normal population (11). In a study of 98 female ballet students aged 11 to 18 (12), twenty percent of the sample had abnormal restrained eating scores (ranging from 10% in the 11 to 14 year-old group to over 36% in the 15 to 18 year-olds), and weights overall fell into the lower 50th percentiles for age and height. The older dancers, in fact, reported a desired weight in the lower tenth percentile. Conditions which are associated with weight loss or impaired nutrition tend to delay puberty. Frisch has suggested that the onset of menarche correlates not only with weight (an average critical weight of 47 kg being required), but also with a calculated body fat of about 16 kg. This indicates a need for proportional body fat of 22-24 % (13, 14).

But other factors besides body weight and nutrition appear to be involved in the delayed puberty of exercising adolescents. Warren reported (4), in a study of young ballet dancers, that they weighed much less than their peers at all ages, and had a much lower percentage of body fat. However, when they did reach menarche, they were heavier than the controls and in fact had reached the critical weight and proportion of body fat (as defined by Frisch) at least 4 months beforehand. After menarche, the controls tended to gain weight fairly rapidly while the dancers did not.

The effect of emotional stress is difficult to quantify, but studies contrasting the age of onset of menarche in ballet dancers and young musicians training and performing professionally have shown that the

musicians did not show the same delay in puberty (4). This suggests that "stress" is not, by it self, the reason for delayed development.

The observation that enforced periods of rest during training in adolescents is associated with remarkably rapid pubertal development attests to the significance of a "training effect" in the delay of puberty (15). It is notable that, to the observer, the individuals who showed rapid development were not malnourished. Progression in breast development from Tanner, stage malnourished. Progression in breast development from Tanner stage 2 to stage 4, which normally takes approximately 2 years, was seen to occur in as little as four months.

In this reproductive dysfunction, therefore, nutritional habits, body weight, body composition and some effect from exercise itself all appear to be contributing factors. It seems likely that the neuroendocrine effects responsible are similar to those producing dysfunction in post-pubertal athletes.

(2) Amenorrhea

The first report of an increased incidence of amenorrhea in runners came in 1978 in a report in the Lancet by Feicht and colleagues (16). This questionnaire study indicated that 6 to 43% of college runners were amenorrheic, depending on the weekly mileage run. This was in contrast to a survey of 66 female athletes at the Tokyo Olympics in 1964 (17), when only one reported amenorrhea. Subsequent studies have compared the incidence of amenorrhea in cyclists, swimmers and runners (18), since runners have become stereotyped as the archetypal amenorrheic athletes; these studies have indicated higher than normal incidences of amenorrhea in all groups, but the incidence was much higher in runners. The incidence of amenorrhea increased as the training mileage increased, but in swimmers and cyclists it remained constant at 12% regardless of training distance.

It is tempting to cite exercise it self (and the physical stress involved) as the main reason for the amenorrhea in athletes, but the fact that amenorrheich runners have a higher incidence of previous menstrual irregularities (3, 19) suggests that other factors are involved.

Athletic training is, in most instances, associated with loss of eight and fat - especially those women involved in aerobic exercise. Other medical models demonstrate that weight loss alone, for whatever reason, may lead to anovulation and amenorrhea. Shangold and Levine (19) have demonstrated that runners who are menstruating are heavier than amenorrheich runners. Schwartz and colleagues (3) showed that amenorrheic runners had proportionately less body fat than runners who are menstruating. Possibly the loss of body fat in amenorrheich runners reduces endogenous estrogen production by peripheral aromatization, but since runners tend to have more muscle than controls the aromatizing capacity of muscle (20) may compensate for the loss of fat. Thin women tend to metabolise estrogen by formation of catecholestrogens more than do fat women (21), and catecholestrogens have a reduced estrogen effect by virtue of their short half-life. However, the reason for the association between the amount of body fat and the rhythm of the menstrual cycle is essentially unknown.

Dietary changes are common when women undertake an exercise programme, but no etiologic connection between this and the development of amenorrhea has been made. Assessment of total caloric intake and dietary components in women runners and non-runners has shown that both amenorrheic and cycling runners tend to have higher total caloric intake than non-runners, but that the percentage of diet consumed as protein is diminished in runners and particularly in amenorrheic runners (3). Nevertheless, the total amount of protein consumed is approximately the same in all.

Exercise is undertaken by many women to relieve psychological stress, yet the organization required to allow regular exercise may in some compulsive women produce a net increase in stress. Subjective stress associated with running was evaluated by Schwartz and colleagues (3) and was found to be significantly higher in amenorrheic athletes compared with regularly menstruating runners. Cumming et al (22) reported higher cortisol levels in runners compared with non-runners, and amenorrheic runners had higher levels than eumenorrheic runners-although this may have reflected either an effect of stress or altered steroid metabolism.

A history of pregnancy appears to protect against the subsequent development of athletic amenorrhea (23), and similarly increasing age reduces the likelihood of menstrual dysfunction. Baker and colleagues (24) reported that in runners less than 30 years of age the incidence of amenorrhea was 67%, while in the older age group it was only 9%. These moderators may simply reflect increased hypothalamic maturity associated with age and proven (as opposed to untested) fertility.

(3) Luteal deficiency

Identification of luteal deficiency is an area of controversy, and most reports of luteal phase deficiency have been based on observations of cycle length or basal body temperature charting. Shortening of the luteal phase and reduced mid-luteal

progesterone levels were reported during intensive training in a 30-year-old runner (25). Prior and colleagues reported the histological finding of luteal insufficiency in a woman attempting to conceive while training for a marathon (2). More recently, Reid and colleagues, in a presentation at the Annual Meeting of the Canadian Fertility and Andrology Society (1989), reported normal endometrial histology in premenstrual biopsies from previously sedentary women undertaking an exercise programme. The presence of luteal insufficiency in athletes therefore remains to a large extent unsubstantiated.

Endocrine Changes

(1) Basal hormone levels in athletes.
There are less available data on chronic changes in baseline levels of hormones in athletes than data on acute exercise-associated changes. Amenorrheic runners tend to be hypoestrogenic (26). Of the known endocrinopathies that may cause amenorrhea, no consistent change in basal levels of prolactin or androgens has been reported (23, 24). TSH levels in amenorrheic runners were significantly lower than the levels in non-runners with psychogenic amenorrhea (3). Baker and colleagues (24) found lower levels of estradiol, LH and sex-hormone-binding globulin in amenorrheic runners compared with eumenorrheic runners and non-runners, but Schwartz et al (3) found higher levels of LH in amenorrheic runners compared with eumenorrheic runner sampled in the early follicular phase. The latter group also found a significantly higher estrone to estradiol ratio in amenorrheic runners compared to non-runners, suggesting that estrogen metabolism is altered in these women. They also reported higher levels of DHEA-S in amenorrheic runners compared with amenorrheic non-runners, and their observation of increased cortisol levels in amenorrheic runners suggested that exercise-related amenorrhea is indeed an entity distinct from other forms of amenorrhea.

(2) Acute hormone changes associated with exercise.

Investigation of acute changes in response to exercise is fraught with possible pitfalls which may give misleading results-perhaps explaining why there is some disagreement of findings in this area. Cumming and Rebar (27) have listed some of these possible pitfalls:

(i) method of sampling which may in it self be stressful, e.g. repeated venepuncture
(ii) insufficient time before sampling to allow levels to become basal
(iii) nonstandardization of time of day
(iv) nonstandardization of stage of menstrual cycle
(v) relatively infrequent sampling
(vi) failure to sample during exercise
(vii) use of discontinuous workload with inadequate rest between workloads
(viii) failure to measure a wide range of hormones to allow correlation of change in related groups of hormones.

The results of investigations in this area also will depend on the duration of exercise, and whether the intensity of exercise is static or changing. Wallace (28) has described four different investigation protocols and has related observed hormone changes to the duration and intensity of exercise. Her study (29), which used two 20-minute bouts of exercise (separated by a 12-minute rest period) of 50% and 75% of maximal intensity respectively, did not show any significant hormone increases. Two other study designs, one of constant intensity exercise and the other of constant exercise with an increment after 20 minutes and after 40 minutes, showed hormone increases only after 30 minutes of continuous exercise. The studies of Cumming et al (30) used a graded exercise protocol to maximum capacity, with blood sampling every five minutes, and found increases in hormone levels from the first (five-minute) sample.

Cumming and colleagues (27) found that anticipation of exercise was associated with a rise in LH and testosterone. With the onset of exercise, non-runners showed a decline in cortisol, a change not seen in trained runners, but cortisol levels subsequently rose. Baseline estradiol and estrone levels were significantly lower in amenorrheic runners than in menstruating runners and non-runners. Estradiol levels increased significantly immediately after beginning exercise in untrained runners, but this was not seen in trained runners; conversely, estrone increased with exercise in trained but not untrained runners. Prolactin and growth hormone levels increased with exercise in runners and non-runners, except for a complete lack of prolactin response in amenorrheic runners. Interestingly, only amenorrheic runners show no prolactin response to exercise; even women with psychogenic amenorrhea show an increase in prolactin with exercise.

The data indicate that preparation for exercise is associated with activation of the ACTH-adrenal axis, but few other conclusions can reasonably be drawn. Since the pre-exercise increase in testosterone precedes or at least parallels the rise in LH, the testosterone rise may be a part of the adrenal preparation. The lack of elevation of basal prolactin, and the failure of amenorrheic runners to show elevation of prolactin in response to exercise, indicate that hyperprolactinemia is not the cause of exercise-induced menstrual dysfunction. Bromocriptine in these women does not restore menstrual cycling (26).

Endogenous opioid peptides

The prejudice that endogenous opiate activity (in the "runner's high") is involved in the development of menstrual dysfunction (31) was supported in a study by Carr and colleagues (32), which suggested that peripheral beta-endorphin levels increased with exercise and that the increase was augmented with training. Endogenous opioid peptides lower the frequency of pulsatile GnRH release, and pulse frequency is increased by administration of the opiate antagonist naloxone However, Cumming and Rebar (33) showed no effect of naloxone on basal gonadotropin levels in amenorrheic athletes. This may not be surprising, since in normally cycling women naloxone has no effect on LH levels in the relatively hypoestrogenic early follicular phase - but it does cause increased LH release in the late follicular and luteal phases, when estrogen levels are higher (34). Athletic amenorrhea is a hypoestrogenic state. How to explain the putative involvement of endogenous opioids in athletic amenorrhea, therefore, remains difficult.

Clinical considerations

Women athletes presenting with oligomeorrhea or amenorrhea must be evaluated as for any woman with menstrual irregularity. It is presumptuous and wrong to ascribe all menstrual dysfunction in athletes to their training programme.

The possibility of pregnancy must be considered initially, although women who have seen a clear temporal relationship between vigorous exercise and menstrual irregularity may in fact be less fertile than their unaffected peers. The signiicant endocrine causes of amenorrhea, namely ovarian failure, polycystic ovary syndrome, hyperprolactinemia and thyroid dysfunction, must be ruled out. A basic assessment would include assays of LH, FSH, prolaction and thyroid function (free thyroxine and TSH). Clinical evidence of hyperandrogenism or adrenal disease warrants assays of plasma androgens and cortisol.

The basic test for hypoestrogenism is a progestin withdrawal test. If there is a failure to respond with bleeding to a course of a progestin such as medroxyprogesterone (Provera) 10 mg. daily for 5 days, there is likely to be significant hypoestrogenism.

If the results of investigation are consistent with hypothalamic amenorrhea or oligomenorrhea (i.e. low LH, FSH and prolactin, and normal thyroid function), then the management of the individual depends upon her acceptance of a reduction in the amount of exercise and her fertility desires. If she is seeking pregnancy, the first approach should be a decrease in activity. If this is unacceptable or does not result in restoration of ovulatory cycles, an attempt at ovulation induction using administration of clomiphene citrate is the next step, although if there is significant hypoestrogenism (failure to bleed in response to progestin) the response rate is small. Ovulation induction with pulsatile GnRH or human menopausal gonadotropins (HMG) may be required.

If the woman is not seeking pregnancy, does not require contraception, and bleeds in response to progestin, then periodic progestin administration (at 1-2 month intervals) should be prescribed to prevent the development of endometrial hyperplasia. If she does require contraception, oral contraceptive therapy may be offered if there is no contraindication.

If she does not bleed in response to progestin, the hypoestrogenism thus demonstrated will be associated with accelerated loss of bone density. Once again, a reduction in the amount of exercise may reduce the hypoestrogenism and even allow resumption of menses. Shangold (35) stresses that no data show that the positive effect of exercise on bone is benefical enough to compensate for estrogen deficiency. She recommends therefore that hypoestrogenic amenorrheic athletes be given sequential estrogen-progestin, such as conjugated estrogen 0.625 mg. daily for 25 days per month with medroxyprogesterone 10 mg. for the last ten days of estrogen administration. Alternatively, an oral contraceptive preparation may be used.

Menstrual dysfunction in athletes is usually a matter of concern to them, although they may deny this. The evaluation of amenorrhea or menstrual irregularity in these women must be done carefully and with a maximum of communication and explanation. Some may not accept the notion of hormone administration. Most alteration in their femininity, and if restoration of cycling can be achieved their self-image will be restored. An exploration of the possibility of reducing the amount of exercise is a fundamental step.

REFERENCES

1. *Malina RM. Menarche in athletes: a synthesis and hypothesis. Ann Hum Biol 1983; 10: 1.*
2. *Prior JC, Ho Yuen B, Clement P et al. Reversible luteal phase changes and infertility. Lancet 1982; 1: 269.*
3. *Schwartz B, Cumming DC, Riordan E et al. Exercise-*

associated amenorrhea: a distinct entity? Am J Obstet Gynecol 1981; 141: 662.

4. *Warren MP. The effects of exercise on pubertal progression and reproductive function in girls. J Clin Endocrinol Metab 1980; 51: 1150.*
5. *Frisch RE, Wyshak G, Vincent L. Delayed menarche and amenorrhea in ballet dancers. New Engl J Med 1980; 303: 17.*
6. *Malina RM, Spirduso WW, Tate C, Baylor AM. Age at menarche and selected menstrual characteristics in athletes at different competitive levels and in different sports. Med Sci Sports Exercc 1978; 10: 218.*
7. *Wilmore JH, Brown CN, Davis JA. Bod physique and composition of the female distance runner. Ann NY Acad Sci 1977; 301: 764.*
8. *Sinning WE, Lindberg GD. Physical characteristics of college age women gymnasts. Res Q Am Assoc Health Phys Ed Rec 1972; 43: 226.*
9. *Ledoux M, Birisson G, Peronnet M. Nutritional habits of young female gymnasts. Med Sci Sports Exerc 1982; 14: 145.*
10. *Calabrese LH, Kirkendall DT, Floyd M et al. Menstrual abnormalities, nutritional patterns and body composition in female classical ballet dancers. Phys Sports Med 1983; 11: 96.*
11. *Garner DM, Garfinkel PE. Sociocultural factors in anorexia nervosa. Lancet 1978; 2: 674.*
12. *Brooks-Gunn J, Warren MP. Tha development of eating problems in adolescent dance students: the contribution of maturational Psychological Functioning, Study Group Conference, Society for Research in Child Development. Educational Testing Service, Princeton NJ October 1983.*
13. *Frisch RE, Revelle R. Height and weight at menarche and a hypothesis of menarche. Arch Dis Child 1971; 46: 659.*
14. *Frisch RE, Revelle R, Cook S. Components of weight at menarche and the initiation of the adolescent growth spurt in girls: Estimated total water, lean body weight and fat. Hum Biol 1973; 45: 469.*
15. *Warren MP. Effect of exercise and physical training on menarche. Sem Reprod Endocrinol 1985; 3: 17.*
16. *Feicht CB, Johnston TS, Martin BJ et al. Secondary amenorrhea in athletes. Lancet 1978; 2: 1145.*
17. *Zaharieva E. Survey of sportswomen at the Tokyo Olympics. J Sports Med Phys Fitness 1965; 5: 215.*
18. *Sanborn CF, Martin BJ, Wagner WW. Is athletic amenorrhea specific to runners? Am J Obs Gynecol 1982; 143: 859.*
19. *Shangold MM, Levine Hs. The effect of marathon training upon menstrual function. Am J Obstet Gynecol: 1982; 143: 862.*
20. *Longcope C, Pratt JH, Schneider SH, Fineberg SE. Aromatization of androgens by muscle and adipose tissue in vivo. J Clin Endocrinol Metab 1978; 46: 146.*
21. *Fishman J, Boyar RM, Hellman L. Influence of body weight on estradiol metabolism in young women. J Clin Endocrinol Metab 1975; 41: 989.*
22. *Cumming DC, Strich G, Brunsting LA et al. Hormonal responses to exercise in long-distance runners with normal menstrual cycles or amenorrhea. Soc Gynecol Invest 1982: Abstract 147.*
23. *Dale E, Gerlach D, Wilhite A. Menstrual dysfunction in distance runners. Obstet Gynecol 1979; 54: 47.*
24. *Baker ER, Mathur RS, Kirk RF, Williamson HO. Female runners and secondary amenorrhea: correlation with age, parity, mileage and plasma hormonal and sex-hormone-binding globulin concentrations. Fertil Steril 1981; 36: 183.*
25. *Shangold M, Freeman R, Thysen B et al. The relationship between long-distance running, plasma progesterone and luteal phase length. Fertil Steril 1979; 31: 130.*
26. *DeCree C. Endogenous opioid peptides in the control of the normal menstrual cycle and their possible role in athletic menstrual irregularities. Obstet Gynecol Survey 1989; 44: 720.*
27. *Cumming DC, Rebar RW: Hormonal changes with acute exercise and with training in women. Sem Reprod Endocrinol 1985; 3: 55.*
28. *Wallace JP. Exercise physiology. Sem Reprod Endocrinol 1985; 3: 1.*
29. *Wallace JP, Webb M, Hodgson J. The relationship between acute changes in sex hormones during exercise. Med Sci Sports Exerc 1983; 15: 174.*
30. *Cumming D, Strich G, Brunsting L et al. Acute exercise-related endocrine changes in women runners and non-runners. Fertil Steril 1982; 36: 421.*
31. *Quigley ME, Sheehan KL, Casper RF et al. Evidence for increased dopaminergic and opioid activity in patients with hypothalamic hypogonadotropic amenorrhea. J Clin Endocrinol Metab 1980; 50: 949.*
32. *Carr DB, Bullen BA, Skrimar GS et al. Physical conditioning facilitates the exercise-induced secretion of beta-endorphin and beta-lipotropin in women. New Engl J Med 1981; 305: 560.*
33. *Cumming DC, Rebar RW. Exercise and reproductive function in lomen. Am J Indust Med 1983; 2: 113.*
34. *Quigley ME, Yen SSC. The role of endogenous opiates on LH secretion during the menstrual cycle. J CLIN Endocrinol Metab 1980; 51: 129.*
35. *Shangold MM. Exercise and amenorrhea. Sem Reprod Endocrinol 1985; 3: 35.*

MARMARA MEDICAL JOURNAL
INSTRUCTIONS TO AUTHORS

1. Manuscripts, letters and editorial correspondence should be sent to "Editor, Marmara Medical Journal, Marmara University, Faculty of Medicine, Istanbul-Turkey" by first class mail (airmail for overseas).
2. Submissions considered for publication are received with the understanding that no part of the submission has previously appeared elsewhere in any but abstract form.
3. Manuscripts should be typed double-spaced on standard-size typewriter paper with margins of at least 2.5 cm. This includes references, tables and figure-legends. The original typescript and two high-quality copies of the manuscripts should be submitted.
4. Number pages consecutively in order and place author (s) name, highest degree, institutional affiliations and address below the title.
5. Marmara Medical Journal invites papers on original research, case reports, reviews, short communications for practical applications, letters, editorials, book reviews and announcements. The number of typewritten pages should not exceed 10 for original articles, 12 for reviews, 4 for case reports and 1 for letters.
6. Original articles and research papers should normally be divided into following sections: A. (1) An informative summary for not more than 200 words must be included and should appear at the beginning of the paper. (2) Key words. (3) Introduction. (4) Materials and Methods. (5) Results. (6) Discussion,and (7) References.

   B. References must be typed in double spacing and numbered consecutively as they are cited. The style of references is that of the Index Medicus. List all authors when there are six or fewer, when there are seven or more, list the first three, then "et al". Sample references follow:

   1. Steward JH, Castaldi PA. Uremic bleeding: a reversible platelet defect corrected by dialysis. QJ Med. 1967; 36 : 409 - 23.

   2. Bearn AG. Wilson's Disease. In: Stanbury JB, Wyngaarden JB, Fredrickson DS, eds. The metabolic basic of inherited disease. New York : McGraw - Hill, 1972: 103-50.
7. Tables should be as few as possible and should include only essential data. Tables should be typed in double spacing on separate sheets and have a legend for each. Diagrams or illustrations should be drawn with black Indian ink on white paper and should be given Roman numerals. Each illustration should be accompanied by a legend clearly describing it : all legends should be grouped and typewritteh (double spaced) on a separate sheet of paper. Photographs and photomicrographs should be unmounted high-contrast glossy black-on-white prints and should not be retouched. Each photograph or illustration should be marked on the back with the name (s) of the author (s), should bear on indication of sequence number and the top should be marked with an arrow. All measurements should be given in metric units.
8. Manuscripts are examined by the editorial board usually sent to out-side referees. The editor reserves the right to reject or to return the manuscript to the author(s) for additional changes if all the guidelines and requirements are not uniformly completed. Only two copies of the rejected papers are returned to the author (s).
9. Proofs will be submitted to the author responsible for proof correction and should be returned to the editor within 5 days. Major alterations from the text cannot be accented.
10. Correspondence and communications regarding manuscripts and editorial material subscriptions and payments should be sent to:

    The Editor
    Marmara Medical Journal
    Marmara University, Faculty of Medicine
    Haydarpaşa - Istanbul.