HORMONES AND SPORT

The effects of intense exercise on the female reproductive system

M P Warren and **N E Perlroth**

Department of Obstetrics and Gynecology, Columbia College of Physicians and Surgeons, New York, New York, USA

(Requests for offprints should be addressed to M P Warren, Department of Obstetrics and Gynecology, PH 16–20, Columbia University, 622 West 168th Street, New York, New York 10032, USA)

Abstract

Women have become increasingly physically active in recent decades. While exercise provides substantial health benefits, intensive exercise is also associated with a unique set of risks for the female athlete. Hypothalamic dysfunction associated with strenuous exercise, and the resulting disturbance of GnRH pulsatility, can result in delayed menarche and disruption of menstrual cyclicity.

Specific mechanisms triggering reproductive dysfunction may vary across athletic disciplines. An energy drain incurred by women whose energy expenditure exceeds dietary energy intake appears to be the primary factor effecting GnRH suppression in athletes engaged in sports emphasizing leanness; nutritional restriction may be an important causal factor in the hypoestrogenism observed in these athletes. A distinct hormonal profile characterized by hyperandrogenism rather than hypoestrogenism is associated with athletes engaged in sports emphasizing strength over leanness. Complications associated with suppression of GnRH include infertility and compromised bone density. Failure to attain peak bone mass and bone loss predispose hypoestrogenic athletes to osteopenia and osteoporosis.

Metabolic aberrations associated with nutritional insult may be the primary factors effecting low bone density in hypoestrogenic athletes, thus diagnosis should include careful screening for abnormal eating behavior. Increasing caloric intake to offset high energy demand may be sufficient to reverse menstrual dysfunction and stimulate bone accretion. Treatment with exogenous estrogen may help to curb further bone loss in the hypoestrogenic amenorrheic athlete, but may not be sufficient to stimulate bone growth. Treatment aimed at correcting metabolic abnormalities may in fact prove more effective than that aimed at correcting estrogen deficiencies.

Journal of Endocrinology (2001) **170,** 3–11

Introduction

Women have become increasingly physically active over the past several decades. Research confirming the benefits of exercise, physician endorsement, legislation creating new opportunities for women in sports, societal changes and media attention have all been instrumental in encouraging women to participate in athletics. While exercise provides substantial health benefits, rigorous physical activity is also associated with a unique set of risks for the female athlete.

The female reproductive system is highly sensitive to physiological stress, and reproductive abnormalities including delayed menarche, primary and secondary amenorrhea and oligomenorrhea occur in 6–79% of women engaged in athletic activity. The prevalence of observed irregularities varies with athletic discipline and level of competition (Table 1) (Petterson *et al.* 1973, Feicht *et al.* 1978, Singh 1981, Abraham *et al.* 1982, Shangold & Levine 1982, Brooks-Gunn *et al.* 1987, Glass *et al.* 1987, Sanborn *et al.* 1987).

The reproductive abnormalities observed in female athletes generally originate in hypothalamic dysfunction and disturbance of the gonadotropin-releasing hormone (GnRH) pulse generator, although specific mechanisms triggering reproductive dysfunction may vary across athletic disciplines. The clinical consequences associated with suppression of GnRH include infertility and compromised bone density, which appears to be irreversible.

This article reviews the pathophysiology, clinical consequences and treatment strategies for exercise-associated reproductive dysfunction.

Pathophysiology

Although specific hormonal profiles of athletes with reproductive irregularities may vary across athletic

 Online version via http://www.endocrinology.org
0022–0795/01/0170–003

Table 1 The prevalence of menstrual irregularities (oligomenorrhea and amenorrhea) in different athletic disciplines

	Study	Number of subjects	Percentage with irregularities
General population	Petterson *et al.* (1973)	1862	1·8
	Singh (1981)	900	5·0
Weight-bearing sports			
Ballet	Abraham *et al.* (1982)	29	79·0
	Brooks-Gunn *et al.* (1987)	53	59·0
	Feicht *et al.* (1978)	128	6–43
	Glass *et al.* (1987)	67	34·0
Running	Shangold & Levine (1982)	394	24·0
	Sanborn *et al.* (1987)	237	26·0
Non-weight-bearing sports			
Cycling	Sanborn *et al.* (1987)	33	12·0
Swimming	Sanborn *et al.* (1987)	197	12·0

From Constantini & Warren MP (1994) with permission.

disciplines, exercise-associated reproductive abnormalities generally stem from dysfunction at the hypothalamic level. The hormonal profile of women engaged in sports which emphasize low weight, such as ballet, long-distance running, gymnastics and figure skating, is characterized by hypoestrogenism resulting from disruption of the hypothalamic–pituitary–ovarian axis. Specifically, suppression of hypothalamic pulsatile release of GnRH, which normally occurs every 60–90 min, limits pituitary secretion of luteinizing hormone (LH) and, to a lesser extent, follicle-stimulating hormone (FSH), which, in turn, limits ovarian stimulation and estradiol production. A prolonged follicular phase, or the absence of a critical LH or estradiol surge mid-cycle, results in the mild or intermittent suppression of menstrual cycles observed in these athletes. Very low LH levels result in delayed menarche or primary or secondary amenorrhea (Warren 1980, Baker *et al.* 1981, Loucks *et al.* 1989).

Original hypotheses for reproductive dysfunction in these athletes emphasized body composition and effects of 'exercise stress'; however, mounting evidence suggests that an energy drain incurred by women whose energy expenditure exceeds dietary energy intake is the primary factor affecting GnRH pulsatility. The body composition hypothesis suggests that menarche occurs in girls when body fat rises to 17% of body weight, and menstrual function is lost when body fat decreases to less than 22% of body weight (Frisch & McArthur 1974). Although widely accepted in the lay and clinical communities, the body composition hypothesis is based entirely on correlation rather than experimental evidence (Schneider & Wade 1997). In fact, body composition does not vary significantly between eumenorrheic and amenorrheic athletes (Loucks & Horvath 1984).

Proponents of the exercise stress hypothesis theorize that intensive athletic training activates the hypothalamic–pituitary–adrenal axis, which disrupts GnRH pulsatility and hence menstrual function. However, experiments attempting to induce menstrual dysfunction in women have shown that exercise coupled with caloric restriction effects LH suppression, whereas exercise alone has no effect on LH pulsatility (Loucks 2000).

The suppression of reproductive function in women engaged in sports emphasizing leanness may be a neuroendocrine adaptation to caloric deficit (Warren 1980, Winterer *et al.* 1984). Recent research suggests that the hormone leptin, a protein product of the obesity (ob) gene which is secreted by the adipocyte and which appears to be an independent regulator of metabolic rate (Zhang *et al.* 1994), may be a significant mediator of reproductive function. Leptin levels fluctuate in response to fat stores and energy availability: leptin levels positively correlate with body mass index (BMI) in humans (Macut *et al.* 1998) and are disproportionately lowered in the presence of fasting (Maffei *et al.* 1995). Additionally, the diurnal rhythm of leptin concentration is suppressed in response to low energy intake.

Multiple studies have demonstrated that rodents without an active form of leptin tend to be amenorrheic and infertile (Legradi *et al.* 1997, 1998), and other studies suggest there may be a chronic low leptin level in women below which menstruation does not occur (Kopp *et al.* 1997, Ballauff *et al.* 1999). In fact, low leptin levels have been reported in amenorrheic women when controlling for body fat, and the typical diurnal pattern of leptin concentration in these women is absent (Laughlin & Yen 1997, Weigle *et al.* 1997). Furthermore, leptin receptors have been found on hypothalamic neurons involved in

control of the GnRH pulse generator (Cheung *et al.* 1997); thus leptin may be a critical factor involved in signaling low energy availability to the reproductive axis. Mammals partition energy among five major metabolic activities: cellular maintenance, thermoregulation, locomotion, growth and reproduction (Wade & Schneider 1992), therefore suppression of reproductive function may be a mechanism which allows the body to adapt to a chronic energy deficit.

Pathological eating behavior and negative energy balance are common among women in sports which require the maintenance of very low body weight for enhanced performance or aesthetic appearance (Warren 1983, Rosen *et al.* 1986, Warren & Brooks-Gunn 1989, Brooks-Gunn *et al.* 1988). Both the reproductive and metabolic hormonal profiles of amenorrheic women engaged in these sports closely parallel those of amenorrheic women with eating disorders such as anorexia nervosa (Warren 1983, Schweiger 1991). Nutritional restriction and the associated metabolic adaptations may thus be important causal factors in the menstrual dysfunction of these athletes.

The energy drain theory is inadequate to explain the reproductive dysfunction of women in all athletic disciplines, however. Sports which emphasize strength over leanness, such as swimming and rowing, are not associated with low weight and restrictive eating patterns (Rosen *et al.* 1986, Brooks-Gunn *et al.* 1988, Barr 1991), yet athletes engaged in these sports are vulnerable to menstrual irregularities as well. The endocrine profile of athletes engaged in these sports is characterized by mildly elevated LH levels, elevated LH/FSH ratios and mild hyperandrogenism rather than the hypoestrogenism observed in athletes engaged in sports requiring thinness (Bonen *et al.* 1981, Carli *et al.* 1983, Frisch 1984, Cumming *et al.* 1987, Baker & Demers 1988, Buchanan *et al.* 1988, Constantini & Warren 1995).

Activation of the hypothalamic–pituitary–adrenal axis may occur in this syndrome, resulting in increased levels of androgens, in particular dehydroepiandrosterone sulfate (DHEA-S). Chronically high concentrations of DHEA-S, or the repeated acute elevations of DHEA-S which have been shown to occur in swimmers (Frisch *et al.* 1984, Dulac *et al.* 1986, Rosen *et al.* 1986), may impair follicular development and result in the anovulation or amenorrhea observed in these women. Alternatively, because high levels of androgens positively affect muscle mass and may therefore be advantageous is sports in which power is a major determinant of performance, naturally elevated levels of androgens may be self-selected in these sports (Constantini & Warren 1995). The syndrome observed in these athletes is less common and has been less extensively studied than that observed in athletes engaged in sports which emphasize thinness, and future research is necessary to ascertain whether the hormonal profile of these women is genetically determined or secondary to activation of the adrenal axis.

Clinical consequences

Delayed menarche and altered pubertal progression

Delayed menarche among athletes has been well documented (Zacharias *et al.* 1976, Marker 1979, Frisch *et al.* 1981, Warren *et al.* 1986), particularly among athletes engaged in sports emphasizing low weight (Fig. 1) (Warren *et al.* 1986). Low gonadotropin (LH and FSH) secretion and minimal thelarche (breast development), as defined by Tanner (1962), of premenarchial ballet dancers suggest ballet training during adolescence may prolong the prepubertal state. Progression of pubertal development and onset of menarche in adolescent dancers appear to be related to activity level, with marked pubertal progression and initiation of menses occurring during periods of relative inactivity (Warren 1980). The delay in pubertal progression and menarche may be related to the energy drain typically incurred by these adolescent athletes.

Low leptin levels associated with nutritional insult may play a critical role in the initiation of puberty and onset of menarche. Studies in rats suggest that leptin may regulate the initiation of puberty by suppressing the prothyrotropin (TSH) gene at the hypothalamic–pituitary–thyroid axis (Legradi *et al.* 1997, 1998). Evidence of leptin mutations in humans who exhibit TSH suppression and lack of pubertal development (Clement *et al.* 1998) provides further support for a role for leptin in regulating reproductive function.

The prolonged hypogonadism associated with delayed menarche may favor long-bone growth, resulting in the decreased upper to lower body ratio and increased arm span which has been observed in ballet dancers, in particular (Warren 1980). Alternatively, the physical characteristics associated with late maturation may be more suitable for successful athletic performance, and the prevalence of delayed menarche and associated eunuchoidal proportions among female athletes may simply reflect genetic differences (Malina 1983).

Amenorrhea

The gonadotropin pattern in athletes who develop amenorrhea appears to revert to a premenarchial pattern, although LH is more selectively suppressed than FSH. The reversion of secondary amenorrhea observed among ballet dancers during periods of rest (Warren 1980) suggests a relationship between the discontinuation of menses and activity level and provides further support for the energy-drain hypothesis.

Infertility

The incidence of inadequate luteal phase, anovulation and oligomenorrhea is considerably greater in athletes than non-athletes (Petterson *et al.* 1973, Vollman 1977, Frisch

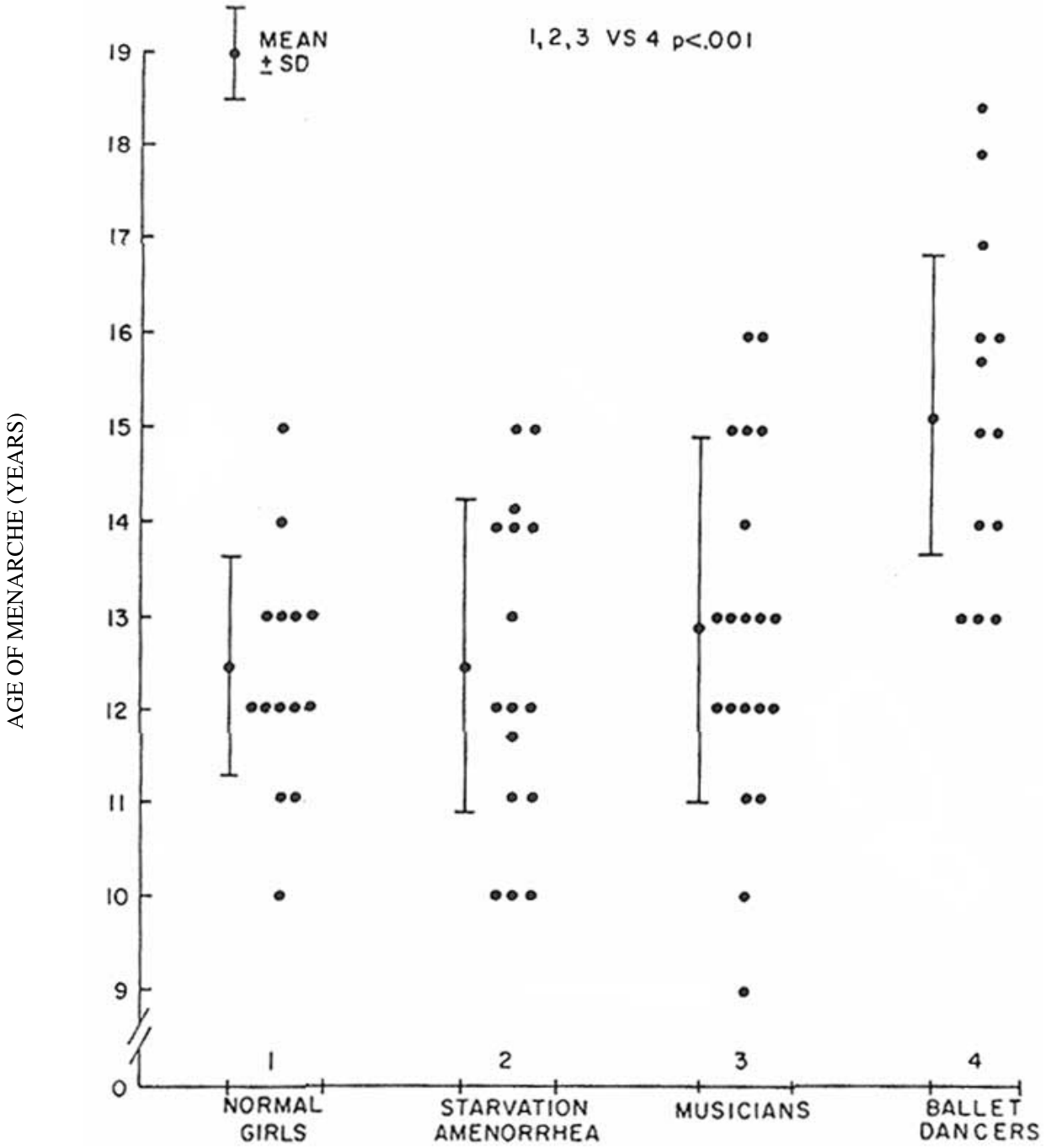

Figure 1 Age of menarche in ballet dancers compared with those in three other groups. From Warren (1980).

et al. 1981, Singh 1981, Highet 1989). The exact incidence of these abnormalities is unknown, however, as many 'eumenorrheic' athletes are actually suffering from hidden menstrual irregularities such as inadequate luteal phase or anovulatory cycles (Shangold *et al.* 1979, Bonen *et al.* 1981, Prior *et al.* 1982, Loucks *et al.* 1989). Dale *et al.* (1979) found that only 50% of runners ovulated during a test month compared with 83% of controls. The incidence of infertility associated with these problems may also be greater than suspected.

Table 2 Markers of bone turnover

		Bone		
	Study (*n*)	Formation	Resorption	Turnover
Model				
Post-menopausal estrogen deficiency	Manolagas & Jilka (1995) (review)	↑	↑	↑
Exercise-induced amenorrhea (runners)	Okano *et al.* (1995) (8)	↓ (osteocalcin)	NA	?
Exercise-induced amenorrhea (runners)	Zanker & Swaine (1998) (9)	↓ (osteocalcin BAP*)	↓ (deoxypyridinoline)	↓

*Bone-specific alkaline phosphate.

Skeletal problems

Reproductive dysfunction resulting from the GnRH suppression observed in athletes engaged in sports emphasizing leanness has its most profound negative impact on the skeleton. Failure to attain peak bone mass, bone loss and failure of weight-bearing bone to mineralize with stress predispose hypoestrogenic athletes to osteopenia and osteoporosis, and increase their risk of scoliosis and bone fracture. Decreased bone density constitutes the final element of the 'female athlete triad', i.e. eating disorders, amenorrhea and osteoporosis.

Forty-eight percent of skeletal mass is attained during adolescence and accumulation continues into the thirties (Benson *et al.* 1985). Bone mass accretion is compromised in late-maturing girls (Dhuper *et al.* 1990, Frusztajer *et al.* 1990, Warren *et al.* 1991), and low bone mineral density has been consistently reported in athletes with hypoestrogenic amenorrhea (Drinkwater *et al.* 1984, Marcus *et al.* 1985, Frusztajer *et al.* 1990). These athletes generally do not attain peak bone mass and may enter menopause with significantly lower bone density than normal women (Highet 1989).

Injuries commonly result from overuse of bone weakened by osteopenia (Myburgh *et al.* 1990, Warren 1992). Numerous studies have shown a correlation between menstrual irregularities and incidence of scoliosis and stress fractures among athletes (Cann *et al.* 1984, Drinkwater *et al.* 1984, Lindberg *et al.* 1984, Marcus *et al.* 1985, Warren *et al.* 1986, Lloyd *et al.* 1987, Barrow & Saha 1988). In one study, scoliosis was reported in 24% of ballet dancers, much higher than that in the general population; 83% of dancers with scoliosis had delayed menarche, whereas only 54% of dancers without scoliosis reported delayed menarche (Warren *et al.* 1986). The prevalence of stress fractures among dancers has been positively correlated with duration of amenorrhea (Warren *et al.* 1986). Similarly, the prevalence of stress fractures and multiple stress fractures has been associated with incidence of menstrual irregularities in runners (Barrow & Saha 1988).

Original theories attempting to explain the well-documented association between hypoestrogenic amenorrhea and bone loss focused on the role of estrogen as a mediator of bone resorption (Cann *et al.* 1984, Drinkwater *et al.* 1984, Marcus *et al.* 1985). However, accumulating evidence suggests that metabolic factors associated with nutritional deprivation may be more important in regulating bone activity. Studies of bone turnover in amenorrheic distance runners have shown a pattern of bone remodeling characterized by reduced bone turnover and reduced bone formation (Okano *et al.* 1995, Zanker & Swaine 1998) rather than the increased bone turnover and increased bone resorption typical of hypoestrogenism (Table 2) (Hergenroeder 1995, Manolagos & Jilka 1995). Acute or chronic energy deficit is known to elicit metabolic aberrations including depressed levels of nutritional markers 3,5,3′-tri-iodothryronine (T_3) and insulin-like growth factor (IGF-I) (Grinspoon *et al.* 1996*a*, Laughlin & Yen 1997). Both T_3 and IGF-I are bone trophic hormones, and their suppression can lead to inadequate bone formation. In fact, estimated energy balance, BMI and serum levels of T_3 and IGF-I correlated positively with serum levels of bone formation markers in the amenorrheic distance runners (Zanker & Swaine 1998). Furthermore, leptin receptors have been found in bone (Bradley *et al.* 1997, Dyson *et al.* 1997), thus depression of leptin levels and suppression of the diurnal leptin rhythm associated with low energy intake may mediate not only reproductive function but also bone accretion. The osteopenia observed in amenorrheic athletes involved in sports emphasizing leanness may therefore be another adaptive response to chronic low energy intake.

Nutritional deprivation in amenorrheic anorectics has been shown to negatively affect attainment of normal skeletal mass (Ward *et al.* 1997). Additionally, restrictive eating habits have been positively correlated with the

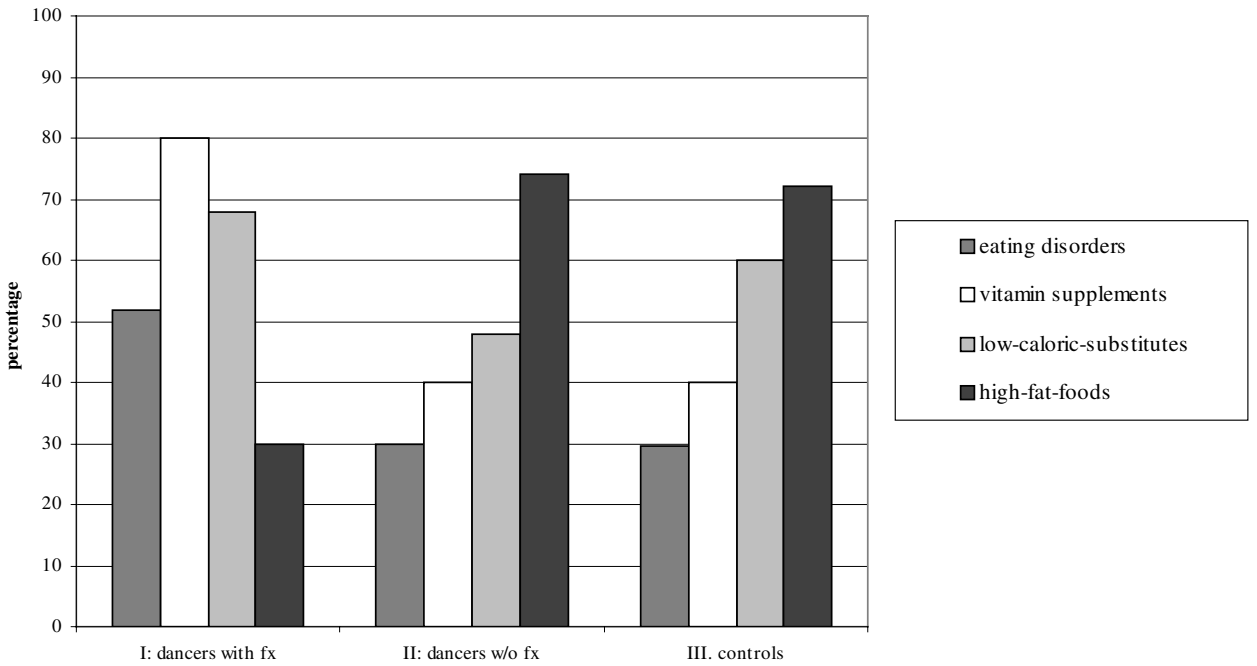

Figure 2 Eating habits of amenorrheic women with and without stress fractures. From Warren *et al.* (1986).

incidence of stress fractures among dancers. In a carefully matched sample of dancers with and without stress fractures, dancers with fractures showed a significantly greater tendency to restrict food intake, manifested by a greater percentage eating less than 85% of the recommended dietary allowance, lower fat intake, higher intake of low-calorie foods and sugar substitutes, and greater incidence of eating disorders (Fig. 2). These patterns emerged irrespective of menstrual abnormalities, which were the same in both groups (Frutzajer *et al.* 1990). Furthermore, it has been suggested that nutritional deprivation and the resulting delay in sexual maturation results in delayed epiphyseal closure of long-bones, which may in turn predispose athletes to scoliosis (Warren 1980).

Weight-bearing exercise has been shown to have a positive impact on bone density of hypoestrogenic postmenopausal women (Notelovitz *et al.* 1991, Karlsson *et al.* 1993, Henderson *et al.* 1995). However, while exercise during a critical adolescent period has been shown to somewhat modulate the negative effects on bone accretion associated with hypoestrogenic amenorrhea, exercise does not sufficiently protect the amenorrheic athlete from bone loss (Kahn *et al.* 1999). The expected increase in bone density of mechanically stressed bone does not occur in amenorrheic dancers and runners (Warren *et al.* 1991, Warren & Holderness 1992).

Diagnosis and treatment

Diagnosis of exercise-associated amenorrhea remains a diagnosis of exclusion. End-organ failure and prolactin-secreting pituitary tumors should be ruled out. Differentiation between hypoestrogenism and hyperandrogenism can be made via patient history and hormonal evaluation.

Often a weight gain of 1–2 kg or a 10% decrease in exercise load (in either duration or intensity) is sufficient to reverse reproductive dysfunction (Prior & Vigna 1985, Drinkwater *et al.* 1986). Many patients will resist this route, however, fearing weight gain or decreased performance. Nutritional counseling may be advised.

Alternatively, ovulation can be induced with clomiphene or GnRH if pregnancy is desired. Oral contraceptives can be administered to regulate menses of oligomenorrheic athletes.

In cases of hypoestrogenic amenorrhea, diagnosis should include careful screening for nutritional insult. Treatment of the possible underlying nutritional deprivation may both restore menses and stimulate bone accretion. Alternatively, hormonal replacement therapy (HRT) may be prescribed to prevent further bone loss, although dosages given to post-menopausal women (0·625 mg for 25 days with 10 mg medroxyprogesterone on days 16–25, followed by 7 days without therapy) appear to be insufficient to curb bone loss (Emans *et al.* 1990, Hergenroeder 1995, Klibanski *et al.* 1995, Warren 1996). Although results have been inconsistent, recent research indicates that higher dose oral contraceptives may effectively prevent further bone loss, but will not replace bone lost prior to intervention. A summary of treatment of hypothalamic amenorrhea is shown in Table 3. In younger amenorrheic athletes, HRT should be administered only after bone growth is complete.

Table 3 Treatment of amenorrhea

	Study	Therapy (*n*)	BMD		
			Spine	Hip	Total
Model					
Hypothalamic amenorrhea (including eating disorders)	Hergenroeder (1995)	Oral contraceptive (5) randomized, 12 months 0·035 mg ethinyl estradiol 0·5–1·0 mg norethindrone	↑	NS	↑
Exercise-induced amenorrhea	Cumming *et al.* (1987)	HRT (8) observed 24–30 months	↑	↑	—
Exercise-induced amenorrhea	Warren *et al.* (1986)	HRT (13) randomized, 24 months	NS	NS	NS
Anorexia nervosa	Klibanski *et al.* (1995)	HRT (22) randomized	NS*	—	—

*Patients with the lowest BMD showed some increase.

Due to the apparent role of metabolic factors in bone accretion, treatment aimed at stimulating osteoblast activity may prove more effective than that aimed at retarding osteoclast activity. Administration of IGF-I to anorexic women has been shown to stimulate a dose-related increase in serum concentrations of bone formation markers (Grinspoon *et al.* 1996*b*). Further research is necessary to determine the most effective treatment strategy for nutritionally linked bone remodeling imbalance.

As bone preservation depends on both calcium intake and bioavailability (Drinkwater *et al.* 1984, Heaney 1987, Dalsky 1990), promotion of a diet rich in calcium and vitamin D is important. Alternatively, calcium (1500 mg) and vitamin D (400 mg) may be given as daily supplements.

Loss of bone mineral density is directly related to duration of amenorrhea (Gulekli *et al.* 1994, Ward *et al.* 1997, Buchanan *et al.* 1988) and appears to be irreplaceable (Drinkwater *et al.* 1990, Bachrach *et al.* 1991, Jonnavithula *et al.* 1993, Guleki *et al.* 1994). It is therefore crucial to restore menses of amenorrheic athletes as soon as possible so as to minimize bone loss and bone complications resulting from osteopenia and osteoporosis.

References

Abraham SF, Beumont PJV, Fraser IS & Llewellyn-Jones D 1982 Body weight, exercise and menstrual status among ballet dancers in training. *British Journal of Obstetrics and Gynaecology* **89** 507–510.

Bachrach LK, Katzman DK, Litt IF, Guido D & Marcus R 1991 Recovery from osteopenia in adolescent girls with anorexia nervosa. *Journal of Clinical Endocrinology and Metabolism* **72** 602–606.

Baker E & Demers L 1988 Menstrual status in female athletes: correlation with reproductive hormones and bone density. *Obstetrics and Gynecology* **72** 683–687.

Baker ER, Mathur RS, Kirk RF & Williamson HO 1981 Female runners and secondary amenorrhea: correlation with age, parity, mileage, and plasma hormonal and sex-hormone-binding globulin concentrations. *Fertility and Sterility* **36** 183–187.

Ballauff A, Ziegler A, Emons G, Sturm G, Blum WF, Remschmidt H & Hebebrand J 1999 Serum leptin and gonadotropin levels in patients with anorexia nervosa during weight gain. *Molecular Psychiatry* **4** 71–75.

Barr SI 1991 Relationship of eating attitudes to anthropometric variables and dietary intakes of female collegiate swimmers. *Journal of the American Dietetic Association* **91** 976–977.

Barrow GW & Saha S 1988 Menstrual irregularity and stress fractures in collegiate female distance runners. *American Journal of Sports Medicine* **16** 209–216.

Benson J, Gillien DM & Bourdet K 1985 Inadequate nutrition and chronic calorie restriction in adolescent ballerinas. *Physician and Sports Medicine* **13** 79–90.

Bonen A, Belcastro AN, Ling WY & Simpson AA 1981 Profiles of selected hormones during menstrual cycles of teenage athletes. *Journal of Applied Physiology* **50** 545–551.

Bradley SJ, Taylor MJ, Rovet JF, Goldberg E, Hood J, Wachsmuth R, Azcue MP & Pencharz PB 1997 Assessment of brain function in adolescent anorexia nervosa before and after weight gain. *Journal of Clinical and Experimental Neuropsychology* **19** 20–33.

Brooks-Gunn J, Warren MP & Hamilton LH 1987 The relation of eating problems and amenorrhea in ballet dancers. *Medicine and Science in Sports and Exercise* **19** 41–44.

Brooks-Gunn J, Burrow C & Warren MP 1988 Attitudes toward eating and body weight in different groups of female adolescent athletes. *International Journal of Eating Disorders* **7** 749–757.

Buchanan JR, Myers C, Lloyd T & Greer RB 1988 Early vertebral trabecular bone loss in normal premenopausal women. *Journal of Bone and Mineral Research* **3** 583–587.

Cann CE, Martin MC, Genant HK & Jaffe RB 1984 Decreased spinal mineral content in amenorrheic women. *Journal of the American Medical Association* **251** 626–629.

Carli G, Aldi VL, Bonifazi M & Lupo Diprisco C 1983 The effect of swimming training on hormone levels in girls. *Journal of Sports Medicine* **23** 45–51.

Cheung CC, Thornton JE, Kuijper JL, Weigle DS, Clifton DK & Steiner RA 1997 Leptin is a metabolic gate for the onset of puberty in the female rat. *Endocrinology* **138** 855–858.

Clement K, Vaisse C, Lahlou N, Cabrol S, Pelloux V, Cassuto D, Gourmelen M & Dina C 1998 A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. *Nature* **392** 398–401.

Constantini NW & Warren MP 1994 Specific problems of the female athlete. In *Clinical Rheumatology, Exercise and Rheumatic Disease*. Eds RS Parish & NE Lane. Philadelphia: Balliere-Tindall.

Constantini NW & Warren MP 1995 Menstrual dysfunction in swimmers: a distinct entity. *Journal of Clinical Endocrinology and Metabolism* **80** 2740–2744.

Cumming DC, Wall SR, Galbraith MA & Belcastro AN 1987 Reproductive hormone responses to resistance exercise. *Medicine and Science in Sports and Exercise* **19** 234–238.

Dale E, Gerlach DH & Wilhite AL 1979 Menstrual dysfunction in distance runners. *Obstetrics and Gynecology* **54** 47–53.

Dalsky GP 1990 Effect of exercise on bone: permissive influence of estrogen and calcium. *Medicine and Science in Sports and Exercise* **22** 281–285.

Dhuper S, Warren MP, Brooks-Gunn J & Fox RP 1990 Effects of hormonal status on bone density in adolescent girls. *Journal of Clinical Endocrinology and Metabolism* **71** 1083–1088.

Drinkwater BL, Nilson K, Chesnut CH III, Bremner WJ, Shainholtz S & Southworth MB 1984 Bone mineral content of amenorrheic and eumenorrheic athletes. *New England Journal of Medicine* **311** 277–281.

Drinkwater BL, Nilson K, Ott S & Chesnut CH III 1986 Bone mineral density after resumption of menses in amenorrheic athletes. *Journal of the American Medical Association* **256** 380–382.

Drinkwater BL, Bruemner B & Chesnut CH III 1990 Menstrual history as a determinant of current bone density in young athletes. *Journal of the American Medical Association* **263** 545–548.

Dulac S, Quirion A, Brisson GR & Decarufel D 1986 Sex differences in serum testosterone response to long-distance swimming. *Hormone and Metabolic Research* **18** 420–421.

Dyson K, Blimkie CJ, Davison KS, Webber CE & Adachi JD 1997 Gymnastic training and bone density in pre-adolescent females. *Medicine and Science in Sports and Exercise* **29** 443–450.

Emans SJ, Grace E, Hoffer FA, Gundberg C, Ravnikar V & Woods ER 1990 Estrogen deficiency in adolescents and young adults: impact on bone mineral content and effects of estrogen replacement therapy. *Obstetrics and Gynecology* **76** 585–592.

Feicht CB, Johnson TS, Martin BJ, Sparkes KE & Wagner WW Jr 1978 Secondary amenorrhea in athletes. *Lancet* **2** 1145–1146.

Frisch RE 1984 Body fat, puberty and fertility. *Biological Reviews of the Cambridge Philosophical Society* **59** 161–188.

Frisch RE & McArthur JW 1974 Menstrual cycles: fatness as a determinant of minimum weight for height necessary for their maintenance or onset. *Science* **185** 949–951.

Frisch RE, Gotz-Welbergen AV, McArthur JW, Albright T, Witschi J, Bullen BA, Birnholz J, Reed RB & Hermann H 1981 Delayed menarche and amenorrhea of college athletes in relation to age of onset of training. *Journal of the American Medical Association* **246** 1559–1563.

Frisch RE, Hall GM, Aoki TT, Birnholz J, Jacob R, Landsberg L, Munro H, Parker-Jones K, Tulchinsky D & Young J 1984 Metabolic, endocrine, and reproductive changes of a woman channel swimmer. *Metabolism: Clinical and Experimental* **33** 1106–1111.

Frusztajer NT, Dhuper S, Warren MP, Brooks-Gunn J & Fox RP 1990 Nutrition and the incidence of stress fractures in ballet dancers. *American Journal of Clinical Nutrition* **51** 779–783.

Glass AR, Deuster PA, Kyle SB, Yahiro JA, Vigersky RA & Schoomaker EB 1987 Amenorrhea in Olympic Marathon runners. *Fertility and Sterility* **48** 740–745.

Grinspoon S, Baum H, Lee K, Anderson E, Herzog D & Klibanski A 1996*a* Effects of short-term recombinant human insulin-like growth factor I administration on bone turnover in osteopenic women with anorexia nervosa. *Journal of Clinical Endocrinology and Metabolism* **81** 3864–3870.

Grinspoon S, Gulick T, Askari H, Landt M, Lee K, Anderson E, Ma Z, Vignati L, Bowsher R, Herzog D & Klibanski A 1996*b* Serum leptin levels in women with anorexia nervosa. *Journal of Clinical Endocrinology and Metabolism* **81** 3861–3863.

Gulekli B, Davies MC & Jacobs HS 1994 Effect of treatment on established osteoporosis in young women with amenorrhea. *Clinical Endocrinology* **41** 275–281.

Heaney RP 1987 The role of calcium in prevention and treatment of osteoporosis. *Physician and Sports Medicine* **15** 83–88.

Henderson NK, Price RI, Cole JH, Gutteridge DH & Bhagat CI 1995 Bone density in young women is associated with body weight and muscle strength but not dietary intakes. *Journal of Bone and Mineral Research* **10** 384–393.

Hergenroeder AC 1995 Bone mineralization, hypothalamic amenorrhea, and sex steroid therapy in female adolescents and young adults. *Journal of Pediatrics* **126** 683–689.

Highet R 1989 Athletic amenorrhea: an update on aetiology, complications and management. *Sports Medicine* **7** 82–108.

Jonnavithula S, Warren MP, Fox RP & Lazaro MI 1993 Bone density is compromised in amenorrheic women despite return of menses: a 2-year study. *Obstetrics and Gynecology* **81** 669–674.

Kahn KM, Warren MP, Stiehl A, McKay HA & Wark JD 1999 Bone mineral density in active and retired ballet dancers. *Journal of Dance Medicine and Science* **3** 15–23.

Karlsson MK, Johnell O & Obrant KJ 1993 Bone mineral density in professional ballet dancers. *Bone and Minerals* **21** 163–169.

Klibanski A, Biller BMK, Schoenfeld DA, Herzog DB & Saxe VC 1995 The effects of estrogen administration on trabecular bone loss in young women with anorexia nervosa. *Journal of Clinical Endocrinology and Metabolism* **80** 898–904.

Kopp W, Blum WF, von Prittwitz S, Ziegler A, Lubbert H, Emons G, Herzog W, Herpertz S, Deter HC, Remschmidt H & Hebebrand J 1997 Low leptin levels predict amenorrhea in underweight and eating disordered females. *Molecular Psychiatry* **2** 335–340.

Laughlin GA & Yen SSC 1997 Hypoleptinemia in women athletes: absence of a diurnal rhythm with amenorrhea. *Journal of Clinical Endocrinology and Metabolism* **82** 318–321.

Legradi G, Emerson CH, Ahima RS, Flier JS & Lechan RM 1997 Leptin prevents fasting-induced suppression of prothyrotropin-releasing hormone messenger ribonucleic acid in neurons of the hypothalamic paraventricular nucleus. *Endocrinology* **138** 2569–2576.

Legradi G, Emerson CH, Ahima RS, Rand WM, Flier JS & Lechan RM 1998 Arcuate nucleus ablation prevents fasting-induced suppression of proTRH mRNA in the hypothalamic paraventricular nucleus. *Neuroendocrinology* **68** 89–97.

Lindberg JS, Fears WB, Hunt MM, Powell MR, Boll D & Wade CE 1984 Exercise-induced amenorrhea and bone densit. *Annals of Internal Medicine* **101** 647–648.

Lloyd T, Buchanan JR, Bitzer S, Waldman CJ, Myers C & Ford BG 1987 The Interrelationship of diet, athletic activity, menstrual status and bone density among collegiate women. *American Journal of Clinical Nutrition* **46** 681–684.

Loucks AB 2000 Exercise training in the normal female. In *Sports Endocrinology*, pp 165–180. Eds MP Warren & NW Constantini. Totowa, NJ: Humana Press, Inc.

Loucks AB & Horvath SM 1984 Exercise-induced stress responses of amenorrheic and eumenorrheic runners. *Journal of Clinical Endocrinology and Metabolism* **59** 1109–1120.

Loucks AB, Mortola JF, Girton L & Yen SSC 1989 Alterations in the hypothalamic–pituitary–ovarian and the hypothalamic–pituitary–adrenal axes in athletic women. *Journal of Clinical Endocrinology and Metabolism* **68** 402–411.

Macut D, Micic D, Pralong FP, Bischof P & Campana A 1998 Is there a role for leptin in human reproduction? *Gynecological Endocrinology* **12** 321–326.

Maffei M, Halaas J, Ravussin E, Pratley RE, Lee GH, Zhang Y, Fei H, Kim S, Lallone R & Ranganathan S 1995 Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. *Nature Medicine* **1** 1155–1161.

Malina RM 1983 Menarche in athletes: a synthesis and hypothesis. *Annals of Human Biology* **10** 1–24.

Manolagos SC & Jilka RL 1995 Bone marrow, cytokines and bone remodeling: emerging insights into the pathophysiology of osteoporosis. *New England Journal of Medicine* **332** 305–311.

Marcus R, Cann CE, Madvig P, Minkoff J, Goddard M, Bayer M, Martin MC, Gaudiani L, Haskell W & Genant HK 1985 Menstrual function and bone mass in elite women distance runners. *Annals of Internal Medicine* **102** 158–163.

Marker K 1979 Zur Menarche von Sportlerinnen nach mehrjahrigem in Training in Kindesalter. *Medizin und Sport* **19** 329–332.

Myburgh KH, Hutchins J, Fataar AB, Hough SF & Noakes TD 1990 Low bone density is an etiologic factor for stress fractures in athletes. *Annals of Internal Medicine* **113** 754–759.

Notelovitz M, Martin D, Tesar R, Khan FY, Probart C, Fields C & McKenzie L 1991 Estrogen therapy and variable resistance weight training increase bone mineral in surgically menopausal women. *Journal of Bone and Mineral Research* **6** 583–590.

Okano H, Mizunuma H, Soda M, Matsui H, Aoki I, Honjo S & Ibuki Y 1995 Effects of exercise and amenorrhea on bone mineral density in teenage runners. *Endocrine Journal* **42** 271–276.

Petterson F, Fries H & Nillius SJ 1973 Epidemiology of secondary amenorrhea: incidence and prevalence rates. *American Journal of Obstetrics and Gynecology* **7** 80–86.

Prior JC & Vigna YM 1985 Gonadal steroids in athletic women: contraception, complications and performance. *Sports Medicine* **2** 287–295.

Prior JC, Ho Yuen B, Clement P, Bowie L & Thomas J 1982 Reversible luteal phase changes and infertility associated with marathon training. *Lancet* **2** 269–270.

Rosen LW, McKeag DB, Hough DO & Curley V 1986 Pathogenic weight-control behavior in female athletes. *Physician and Sports Medicine* **14** 79–86.

Sanborn CF, Albrecht BH & Wagner WW Jr 1987 Athletic amenorrhea: lack of association with body fat. *Medicine and Science in Sports and Exercise* **19** 207–212.

Schneider JE & Wade GN 1997 Letter to the editor. *American Journal of Physiology* **273** (*Endocrinology and Metabolism* **36**) E231–E232.

Schweiger U 1991 Menstrual function and luteal-phase deficiency in relation to weight changes and dieting. *Clinical Obstetrics and Gynecology* **34** 191–197.

Shangold MM & Levine HS 1982 The effect of marathon training upon menstrual function. *American Journal of Obstetrics and Gynecology* **143** 862–869.

Shangold MM, Freeman R, Thysen B & Gatz M 1979 The relationship between long-distance running, plasma progesterone, and luteal phase length. *Fertility and Sterility* **31** 130–133.

Singh KB 1981 Menstrual disorders in college students. *American Journal of Obstetrics and Gynecology* **1210** 299–302.

Tanner JM 1962 *Growth and Adolescence*. Oxford: Blackwell Scientific.

Vollman RF 1977 *Menstrual Cycle (Major Problems in Obstetrics and Gynecology Series)*, vol 7. Baltimore: WB Saunders.

Wade GN & Schneider JE 1992 Metabolic fuels and reproduction in female mammals. *Neuroscience Biobehavioral Review* **16** 235–272.

Ward A, Brown N & Treasure J 1997 Persistent osteopenia after recovery from anorexia nervosa. *International Journal of Eating Disorders* **22** 71–75.

Warren MP 1980 The effects of exercise on pubertal progression and reproductive function in girls. *Journal of Clinical Endocrinology and Metabolism* **51** 1150–1157.

Warren MP 1983 The effects of undernutrition on reproductive function in the human. *Endocrine Reviews* **4** 363–377.

Warren MP 1992 Amenorrhea in endurance runners [Clinical Review 40]. *Journal of Clinical Endocrinology and Metabolism* **75** 1393–1397.

Warren MP 1996 Evaluation of secondary amenorrhea [Clinical Review 77]. *Journal of Clinical Endocrinology and Metabolism* **81** 437–442.

Warren MP & Brooks-Gunn J 1989 Delayed menarche in athletes: the role of low energy intake and eating disorders and their relation to bone density. In *Hormones and Sport*, vol 55, pp 41–54. Eds Z Laron & AD Rogol. New York: Serono Symposia Publications from Raven Press.

Warren MP & Holderness CC 1992 Estrogen replacement does not affect bone density with one year of replacement (abstract 425). *Endocrine Society Annual Meeting*, 24–27 June, 1992. San Antonio, TX, USA.

Warren MP, Brooks-Gunn J, Hamilton LH, Warren LF & Hamilton WG 1986 Scoliosis and fractures in young ballet dancers: relation to delayed menarche and secondary amenorrhea. *New England Journal of Medicine* **314** 1348–1353.

Warren MP, Brooks-Gunn J, Fox RP, Lancelot C, Newman D & Hamilton WG 1991 Lack of bone accretion and amenorrhea: evidence for a relative osteopenia in weight bearing bones. *Journal of Clinical Endocrinology and Metabolism* **72** 847–853.

Weigle DS, Duell PB, Connor WE, Steiner RA, Soules MR & Kuijper JL 1997 Effect of fasting, refeeding, and dietary fat restriction on plasma leptin levels. *Journal of Clinical Endocrinology and Metabolism* **82** 561–565.

Winterer J, Cutler GB Jr & Loriaux DL 1984 Caloric balance, brain to body ratio, and the timing of menarche. *Medical Hypotheses* **15** 87–91.

Zacharias L, Rand WM & Wurtman RJ 1976 A prospective study of sexual development and growth in American girls: the statistics of menarche. *Obstetrical and Gynecological Survey* **31** 325–337.

Zanker CL & Swaine IL 1998 The relationship between bone turnover, oestradiol, and energy balance in women distance runners. *British Journal of Sports Medicine* **32** 167–171.

Zhang Y, Proenca R, Maffei M, Barone M, Leopold L & Friedman JM 1994 Positional cloning of the mouse obese gene and its human homologue. *Nature* **372** 425–432.

Received 11 September 2000
Accepted 9 February 2001