Deficiency of energy balance and ovulatory disorders

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The effect of unbalanced nutrition on the menstrual cycle in women has largely been investigated in epidemiological studies and was illustrated by the observation that the Bushman women ovulated only at a certain time of the year when food is plentiful and hunting activities restricted (Vander Walt et al., 1978). In clinical studies, food deprivation clearly induces overt abnormalities of the puberty and ovulatory processes (Reid and Van Vugt, 1987; Bringer et al., 1990). Experimental studies in various animal models have confirmed the profound impact of food restriction and/or underweight on gonadotrophin concentrations, mainly by altering the release of gonadotrophin-releasing hormone (GnRH). The cult of a slim body and dieting, or the selection habits it creates, are extremely common in Western societies. Their influence on puberty, menstrual cycle and female fertility is obvious. A vegetarian low caloric diet may rapidly induce cycle disorders and a short luteal phase (Pirke et al., 1986). Disturbances in the pulsatility of gonadotrophic hormones are responsible for anovulation and they occur rapidly when caloric restriction and/or slimness with excessive loss of fat mass are associated with psycho–socio–professional stress factors or intensive sporting activities. Low weight and fat mass, low calorie intakes, eating disorders, hyperactivity and psychological stress have been evoked to explain abnormalities of cycles and fertility observed in many women.

Frequently, these conditions are associated factors in the development of menstrual disturbances and the crucial role or relative importance of a specific cause can be questioned (Figure 1). The apparent miscellaneous environmental aetiologies involved in hypothalamic–pituitary dysfunction may operate by a common mechanism. An inadequacy between nutritional needs and available energy balance represents a realistic hypothesis for explaining the dysregulation of anovulation met in most ‘environmental disorders’ of menstrual cyclicity.

Does psychological stress play a key role in cycle disturbances associated with nutritional disorders?

Psychological stress, anxiety, panic attacks, depression, and major life events have been implicated as causes of an occasional missed period. However, a number of studies have established that emotional upsets do not contribute to prolonged amenorrhoea over a long-term period (Fries et al., 1974; Schachter and Shoham, 1994). Psychological indicators of stress similarly appeared in matched eumenorrhoeic and amenorrhoeic runners (Loucks and Horvath, 1985). Therefore, it seems more likely that metabolic or nutritional stress is the essential determining factor, although psychological stress is a permissive factor. Amenorrhoea is not observed in most women with panic attacks or chronic anxiety and is only reported in 30–50% of patients with bulimia nervosa (Russel, 1979; Pirke et al., 1987). In contrast, underweight women with anorexia nervosa are constantly amenorrhoeic. It is difficult to assert that the difference in intensity of psychological stress between these three groups is able to explain the various prevalences of amenorrhoea observed in each one. The notion that bulimic patients with impaired follicular development were significantly leaner than bulimic women...
with normal cycles supports the hypothesis of the major role of weight deficit and caloric intakes (as seen in many bulimic-vomiting patients) in chronic cycle disturbances occurring in stressed women. Two recent reports strongly suggest that in monkeys, signals that suppress the normal secretory mode of luteinizing hormone (LH) during acute fasting reflect the metabolic status of the body during the transition from a fed to a fasted state, rather than psychological stress (Schreinhofer et al., 1993a). Crisp (1965) observed that the anorectic patients were often restless, slept badly, and typically suffered from early morning waking and/or waking in the middle of the night. This assertion demonstrates the difficulties of individualizing the psychological stress from other factors, i.e. hyperactivity and nutritional disorders. An obsession with performance and activity plus an excessive sensitivity to psychological contraints and, above all, high expectations for body image are commonly seen in the restricted and stressed Western women. Together, these all act to reinforce the process impairing the gonatotrophic–ovarian axis.

**Low body weight and low fat are not the main factors involved in nutritional dysfunctions of the menstrual cycle**

Pubertal delay, menstrual cycle abnormalities, ovarian dysfunction and infertility among women are associated with excessive weight loss and low body fat content (Frisch, 1978, 1987, 1988; Scott and Johnston, 1982; Reid and Van Vugt, 1987; Schweiger et al., 1987). A correlation was found between both body weight and body fat and reproductive function in both young girls and women. Although critical body weight and fat mass may be one prerequisite for normal reproduction, factors other than body weight and composition are clearly involved. Low body fat is not invariably associated with menstrual irregularity in the human (Sinning and Little, 1987; Sanborn et al., 1987) as seen in constitutionally low weight women with normal cycles. A substantial number of anorectic girls do not resume menstrual function within a year of weight restoration within the normal range (Schweiger et al., 1989). Mild caloric reduction diets will cause menstrual irregularities in the majority of normal weight young women, even when their body weight does not fall below 100% of the ideal body weight (Pirke et al., 1989; Schweiger et al., 1992). Vegetarian diets affect the cycle more than a non-vegetarian diet, when both induce the same weight loss (Pirke et al., 1986).

For a similar mean body mass index (BMI), 27% of the severe dieters ovulated compared with 100% of the non-dieters, over a similar one-cycle observation period (Rock et al., 1996). In most previous studies (Bronson and Manning, 1989; Bringer et al., 1989; Snow et al., 1990; Luke and Schoeller, 1992), a reduction in dietary fat intake (to <25% of energy) associated with reduced total energy and increased dietary fibres intakes, has been observed to promote reduced circulating oestrogen concentrations and altered hormonal patterns in the menstrual cycle.

Most of the animal studies found no evidence to support the exclusive body fat hypothesis (Morin, 1986; Schneider and Wade, 1989; Bronson and...
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Manning, 1991). In hamsters, anoestrus was not caused by changes in any dimension of body size per se, but instead by the availability of metabolic fuels (Schneider and Wade, 1989). Lean hamsters were more susceptible to starvation-induced anoestrus than fat hamsters (Schneider and Wade, 1989). Simultaneous pharmacological blockage of fatty acid oxidation and glycolysis inhibited reproduction but, as long as one of these metabolic pathways could be used, oestrous cycles continued (Schneider and Wade, 1989). Thus, reproduction in female Syrian hamsters is sensitive to the general availability of oxidizable metabolic fuels. Although body fat stores can buffer the effects of starvation on oestrous cyclicity, there is no data in this animal model which support the notion that there is a critical body weight or composition necessary for reproduction (Schneider and Wade, 1989). The majority of studies in rodents and larger animals argue strongly against the proposition that ovulation can mainly be regulated by body fat (Glass et al., 1979; Perrigo and Bronson, 1983; Hansen et al., 1983; Bronson, 1987; Armstrong and Britt, 1987). In rhesus monkeys, no relationship was observed between body fat, as measured by thickness of the abdominal skinfold, and pubertal ovulation.

This review suggests that body fat does not play the central role in the regulation of ovulation, in contrast to the previous hypothesis of Frisch and McArthur (1974).

Nutritional status plays an essential role in menstrual dysfunction observed in athletes

Female athletes involved in endurance training frequently develop menstrual disturbances (Cummings, 1987, 1989). Exercise amenorrhoea is more common in some sports, e.g. running, ballet and gymnastics, than in others (Warre, 1980, 1989; Fernstrom, 1983; Loucks and Horvath, 1985; Glass et al., 1987; Cummings, 1989; Mansfield and Emans, 1989; Kaiseraver et al., 1989). Competitive athletes have several factors that might contribute to their hypothalamic-ovarian dysfunction: intensity of physical exercise, stress, decreased body fat and diet have all been evoked as possible contributing factors (Cummings, 1989; Mansfield and Emans, 1989; Bergendahl and Veldhuis, 1995). Studies to determine whether increasing mileage enhanced frequency of amenorrhoea have given conflicting results (Cummings, 1989). The influence of increased training is inconsistent in dancers and runners and less frequent in swimmers (Sanborn et al., 1987; Warre, 1989; Schweiger, 1989 et al.).

Prospective studies have shown that most women who have regular menses continue to do so with increased intensity of training (Cummings, 1989). Busy schedules pushing exercise for competition would cause psychological stress. In a study, amenorrhoeic runners reported greater stress related to their competitions than eumenorrhoeic runners (Schwartz et al., 1981). In contrast, most evaluations of psychological well-being found little or no difference between amenorrhoeic and normally-menstruating runners (Warre, 1980; Schwartz et al., 1981; Galle et al., 1983). Ballet dancers had delayed a menarche whereas music students, presumably under similar competitive stress, did not (Warre, 1980; Foster and Olster, 1985). Numerous data have shown no evidence that the prolonged menstrual irregularity met in physical hyperactivity is caused by psychological stress alone; this appears to be mainly implicated in transient disorders of the menstrual cycle.

Many athletes limit their nutritional intake in sports in which low body fat is perceived to have a competitive advantage, e.g. running, ballet dancing or gymnastics (Mansfield and Emans, 1989). However, menstrual disturbances are not invariably associated with reduced body fat. Total caloric intakes can be very low for the level of activity of these athletes (Frisch, 1981). For example, in amenorrhoeic competitive runners, daily food intakes reached 1700 kilocalories while the eumenorrhoeic runners with a similar BMI consumed 2200 kilocalories (Frisch et al., 1981).

In amenorrhoeic athletes, nutritional inadequacies are frequently observed, sometimes coupled to weight-loss and sometimes not. The amenorrhoeic runners had significantly lower caloric intakes and took less fat and red meat than regularly menstruating runners (Brooks et al., 1984; Hill et al., 1986; Jones et al., 1987; Kaiseraver et al., 1989). Although sedentary subjects had similar caloric intakes to amenorrhoeic runners, they
differed in having a higher dietary amount of fat and red meat (Brooks et al., 1984; Kaiseraver et al., 1989).

Thus the amenorrhoeic runners had a metabolic deficit resulting from an inadequate calorie intake with regard to daily calorie expenditure. The absence of weight loss in a longitudinal survey of these competitors raises the possibility that their basal metabolic rates have been reduced through food restriction, improper dietary habits and/or exercise training. Cynomolgous monkeys trained to run developed dysovulatory cycles and amenorrhoea and they did not lose weight in spite of constant food intakes (Cameron, 1989). This observation and others in animals supported the concept that the adaptative reduction of basal energy expenditure could be a common signal for the suppression of pulsatile gonadotrophin secretion in food restriction combined with a high level of physical activity. In summary, the results of many investigations support the observations that nutritional inadequacy and/or energy unbalance coupled with intense exercise contribute to the hypo-gonadotrophic amenorrhoea seen in athletes.

Is the influence of dieting on menstrual cyclicity the result of deficiency of calories or those of a specific nutrient?

A short 4 day dietary restriction in normal weight women affected LH pulsatility (Loucks and Heath, 1994; Olson et al., 1995), although a major impact on ovulation and menstrual function required a longer duration of dieting (Olson et al., 1995). The observation that vegetarian diets (Pirke et al., 1986) with low protein content disrupted the cycle more than a non-vegetarian diet causing the same weight loss, has evoked the possible role of specific nutrients on ovulatory regulation in the human (Pirke et al., 1986). However, considerable animal research supports the idea that suppression of reproductive function during under-nutrition is not due to a deficiency in a particular dietary nutrient but is the result of a deficiency of calories (Foster and Olster, 1985; Foster et al., 1989). In the restricted rat, as in the semistarved lamb, it is remarkable that a single meal can override the suppressed secretion, with appearance of high-amplitude LH pulses a few hours after eating their one daily meal (Foster et al., 1989; Bronson and Manning, 1989, 1991).

After 6–9 weeks of isocaloric protein deficient diet consumption, monkeys maintained normal circulating LH and follicle stimulating hormone (FSH) concentrations suggesting that a deficiency of dietary protein does not provide the signal leading to reproductive impairment in restricted monkeys (Cameron, 1989; Figure 2). Similar experiments showed that neither fat nor carbohydrate deficiencies resulted in a suppression of circulating gonadotrophin concentrations (Cameron, 1989). In the same way, the essential impact of total calorie intake, rather than a specific nutrient, was further confirmed by the ability of a normo-caloric protein-deficient diet to restore normal gonadotrophin secretion in previously restricted monkeys (Cameron, 1989).

Which is the mechanism of nutritional ovulation regulation?

The data presented above clearly point out that caloric deficiency is the main factor involved in chronic dysregulation of ovulation induced by numerous environmental events. More exactly, the adequacy between availability of metabolic fuels from external sources (food intakes) or from internal reserves (fat mass) and the requirements for energy expenditure by physical activity appear to be essential to maintain gonadotrophin-ovarian function. The mechanism by which the GnRH pulse generator, and subsequently LH and FSH secretion, can be modulated by energy balance is unknown. Several candidates could be implicated as the ‘common link’ provoking the cycle disorders: (i) alterations in metabolic fuels such as free fatty acids, amino acids and glucose; (ii) decrease in peripheral hormones such as insulin, insulin-like growth factor (IGF)-I and leptin; (iii) impairment of neurohormonal signals; and (iv) chronic reduction of basal metabolic rate and thermogenesis which could affect hypothalamic secretion by changes in vasular flow and/or neurosecretion.

Influence of metabolic fuels on reproduction

This is apparent in animal models where ovulation depends upon the availability of oxidizable fuels,
Figure 2. Luteinizing hormone (LH) concentrations in monkeys. These decrease during reduced food intake and do not appear to be affected by the deficiency of one specific nutrient (protein, fat, carbohydrate). Taken from Cameron (1989).

such as glucose and fatty acids (Cahill et al., 1966). Acute starvation blocks the oestrous cycle of the Syrian hamster, an effect that can be countered by adding glucose to the drinking water (Morin, 1986). Concerning the role of metabolic fuels generated by endogenous reserves located in body fat, it is remarkable that lean hamsters were more susceptible to starvation-induced anoestrus than fat hamsters (Schneider and Wade, 1989). The striking influence of the general availability of metabolic fuels, rather than those of any one specific fuel have been reinforced by experiments in hamsters showing the necessity of a simultaneous pharmacological blockade of both fatty acid oxidation and glycosis to inhibit reproduction (Schneider and Wade, 1989). In the gonadectomized lamb, peripheral i.v. adminsitration of the glucose antagonist 2-deoxyglucose (2DG) causes a transient decrease of LH pulse frequency but not LH pulse amplitude, which can be prevented by GnRH injection (Bucholtz et al., 1996). These results suggest that glucose availability affects LH pulse frequency by acting with the central nervous system to modulate GnRH secretion (Bucholtz et al., 1996).

Peripheral hormones as a link between nutritional status and reproduction: the role of insulin, IGF-I, and leptin

A plausible concept remains that insulin provides an important signal to the brain and to the hypothalamic structures in response to the changes in food intake and body composition (Bergendahl and Veldhuis, 1995). Insulin could act in the central nervous system to modulate the activity of the hypothalamic neurons or at the pituitary level by increasing the sensitivity of gonadotropes to GnRH (Van Houten et al., 1979; Baskin et al., 1983). Insulin-binding sites are located in the median eminence (Van Houten et al., 1979; Baskin et al., 1983). The Glut-4 hypothalamic expression confirms the possibility of a glucose and insulinsensing mechanism of the neuroendocrine cells located in this area (Livingstone et al., 1995). Insulin has direct stimulatory effects on the electrical activity of hypothalamic neurons in the rat (Bergendahl and Veldhuis, 1995) and indirectly can affect the availability of amino acid precursors of neurotransmitter synthesis in the brain (Fernstorm, 1983). Insulin administration during fasting enhances the transport of tryptophan and further increases the brain content of serotonin, which affects LH secretion (Fernstorm, 1983).

Thus malnutrition, eating disorders and body composition could modify gonadotrophin secretion by modulating insulin and IGF-I concentrations (Counts et al., 1992). Both insulin and IGF-I values were reported to be low during nutritional deprivation in anorexia nervosa patients and were restored by refeeding (Schreiber et al., 1991). Influence of the changes in IGF-I concentrations at the hypothalamic-pituitary level is hypothetical.
while its role at the ovarian level remains controversial in clinical conditions. On the other hand, conflicting results render unproven the hypothesis of the essential role of glucose and insulin. Cerebroventricular infusion of insulin had no effect on LH secretion in underfed lambs and it decreased LH pulsing in fed females (Hilerman et al., 1993).

Leptin, a protein encoded by the \textit{ob} gene that is expressed in adipocytes, regulates eating behaviour via central neuroendocrine mechanisms. Injection of leptin into \textit{ob/ob} mice increases the concentration of circulating gonadotrophins (Barash et al., 1996), promotes ovarian follicular development (Barash et al., 1996), and restores fertility (Chelab et al., 1996). Therefore, leptin could be one of the missing peripheral links between nutritional status and the process which regulates reproductive function. The discovery of leptin receptor mRNA in the brain and the ovary (Cioffi et al., 1996) suggests that leptin may act centrally to alter hypothalamic and/or pituitary functions and that leptin may promote ovarian function through direct action on the ovarian follicle. In women, the change in fat mass is significantly correlated with the change in leptin (Kohrt et al., 1996) and weight gain induces a rise in circulating leptin concentrations (Kolaczynski et al., 1996). Plasma leptin is significantly reduced by 26% in subjects who consumed a 1000 kcal diet for 10 days (Ostlund et al., 1996). Leptin concentrations are reduced in association with low weight and percentage body fat in subjects with anorexia nervosa (Figures 3 and 4; Grinspoon et al., 1996). Together these data provide evidence that alterations of leptin in nutritional disorders may be a signal modulating the reproductive axis mainly in directly affecting the hypothalamus and/or pituitary secretory patterns.

Other possible mechanisms influencing the hypothalamic GnRH pulse generator are the variations of neurally active amino acids such as glutamate, aspartate, \(\gamma\)-aminobutyric acid (GABA), glutamine and alanine (Tal et al., 1983; Ebling et al., 1990). Plasma concentrations of excitatory amino acid glutamate, which is known to stimulate LH secretion, have been shown to decrease during reduced food intake (Tal et al., 1983) and a bolus of aspartate derivatives given to hypogonadotrophic lambs on a restricted diet results in increased LH plasma concentrations (Ebling et al., 1990). The same stimulatory effect of aspartate on LH concentrations was observed in lambs previously submitted to gluco-deprivation lowering LH secretion (Bucholtz et al., 1996).

\textbf{Neurohormonal mechanisms of gonadotrophin dysregulation}

In deprivation states, this remains highly speculative. Since corticotrophin-releasing hormone (CRH) administration can decrease pulsatile LH release putatively by suppressing GnRH secretion, one possibility is that hypogonadotrophism induced by
fasting or certain stresses is due to an increased inhibitory activity of CRH on the GnRH pulse generator (Barbarino et al., 1989). The role of endogenous opioid peptides, among them β endorphin, which first increase and then decrease during fasting have not been determined (Bergendahl and Veldhuis, 1995). Although the concentrations of norepinephrine and dopamine gradually increase in the body periphery during acute fasting, the specific role of catecholamines in the regulation of the gonadotropes during malnutrition is not known (Bergendahl and Veldhuis, 1995). Neuropeptide Y (NPY) gene expression in the brain and its concentration in hypothalamus have been found elevated during malnutrition without demonstrating a direct role for NPY in decreased GnRH secretion (White and Kershaw, 1990).

Table I. Clinical features at baseline (n = 20)

<table>
<thead>
<tr>
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<th>Mean ± SD</th>
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<tr>
<td>Age (years)</td>
<td>23.8 ± 8.07</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>35.28 ± 6.87</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.60 ± 0.06</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>13.78 ± 2.11</td>
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The hypothetical role of the 5-HT neurotransmitter system is highly ambiguous in fasting-induced hypogonadotrophism (Bergendahl and Veldhuis, 1995). The plausible influence of the vagal nerve in regulating secretion of LH during food restriction is suggested by the observation that complete vagotomy and gastric vagotomy restore the fasting-induced suppression of pulsatile LH release in ovariectomized oestradiol-treated female rats (Cagampang et al., 1992). The changes in gastro-intestinal luminal contents during fasting could modify mechanoreceptors and chemo-receptors and therefore transmission of the signals suppressing LH output.

Is low basal metabolic rate implicated in menstrual cycle disturbances occurring in restricted and/or hyperactive women?

This review suggests that ovulation can largely be regulated in relation to energy balance. The amounts of energy available from the food or stored in adipose tissue are important components of energy balance, as are both basal and exercise energy expenditures. The last is increased by hyperactivity frequently seen in hypothalamic amenorrhoea, while energy supply by food is frequently found inadequate in these women, in regards to the high requirements.

Basal metabolic rate (BMR), so called resting energy expenditure (REE), is usually the largest component of an individual’s total daily energy expenditure. In the normally fed human, BMR is highly correlated with the fat free mass, which is mainly composed of the metabolically active body cell mass (Luke and Schoeller, 1992). Therefore in the normally nourished individual, the resting energy expenditure can be predicted from evaluation of fat free mass (pREE). However in restricted food supplies, REE assessed (aREE) by indirect calorimetry (based on O₂ consumption with the conversion factor of 4.82 kcal/l O₂) is lower than the predicted REE (aREE < pREE) (Luke and Schoeller, 1992).

A lower aREE than pREE is a strong indicator of an inappropriate calorie intake and testifies to down-regulation due to a negative energy balance and an inadequacy between the caloric intakes and requirements. To investigate the hypothesis that basal metabolic rate and thermogenesis could be involved as regulators of gonadotrophin secretion, we assessed by indirect calorimetry the relationship between plasma LH and FSH concentrations and resting metabolic rate in 20 women with anorexia nervosa aged 14–38 years (Lefebvre et al., 1995). The patients had been admitted voluntarily and consented to the overall treatment regimen. Subjects were non-medicated, had no endocrinopathic diseases, and met established criteria for anorexia nervosa (DSM III); all were amenorrhoeic. They were evaluated at baseline and 10 of them were followed during spontaneous or enteral renutrition and evaluated 6–10 weeks later. Study group characteristics at baseline are shown in Table I.

Body composition analysis

Physical examination included several anthropometric measurements: body weight was measured to the nearest 0.1 kg, and body height was recorded in centimetres. The BMI was calculated (weight in kg/height in m²). To assess the body composition, whole body bioelectrical impedance...
analysis (BIA) was conducted in all subjects, using a portable impedance analyser (Akern Bia 101/S, Lab Eugedia, France).

**Endocrine and metabolic investigations**

Hormonal status included dosage of plasma LH, FSH, total and free testosterone, androstenedione, dihydroepiandrosterone sulphate (DHEAS) and sex hormone binding globulin (SHBG) after overnight fasting. GnRH (100 μg) was injected i.v. and blood samples for LH and FSH determinations were obtained at basal conditions and 15, 30 and 60 min after bolus. The sum of LH (LH 0 + LH 15 + LH 30 + LH 60) was used to assess the gonadotrophin secretion. LH, FSH, SHBG and androstenedione were assessed by radioimmunoassay (Coatria Biomerieux), testosterone, SHBG and DHEAS were assessed by radioimmunoassay (Biomérieux, Lyon, France).

Resting metabolic rate (RMR) was assessed (a RMR) after the subjects fasted overnight. The subjects were asked to remain motionless and awake during the test. Metabolic rate was determined by an indirect calorimeter (Deltatrac*, Datex SA, Helsinki, Finland). The resting metabolic rate was determined as the mean energy expenditure during 30 min, at least 10 min after placement of the hood. The resting metabolic rate may also be predicted (pRMR) using the Harris-Benedict’s equation. Assessments of body composition, endocrine and metabolic investigations were all performed on the same day. All statistical analyses were carried out using SAS statistical software. Values are expressed as the mean ± SD. The Spearman test was used to evaluate correlations. Multiple regression analyses were carried out using predictor variables of primary interest if they exhibited independent predictive power for the outcome variable in question. BMI, fat weight (FW), lean weight (LW) LH 0, DHEAS, resting metabolic rate (RMR) were included in multiple regression analysis to explain LH secretion (S LH).

At baseline, anorectic women had a low fat mass and the REE assessed from indirect calorimetry was 21% lower than the pREE fat-free mass (927 ± 191 versus 1169 ± 80 kcal/24 h) (Table II).

Prior to refeeding, average LH concentration was markedly reduced while FSH was low although less altered (Table III). During renutrition, multivariate analysis showed that a REE appeared to be the closest factor related to LH response to GnRH \((r = 0.61, P < 0.0001; \text{Figure 5})\) with a greater correlation than BMI \((r = 0.40, P < 0.05)\) or body fat \((r = 0.42, P < 0.01)\). These results support the hypothesis of the energetic regulation of gonadotrophin secretion. It is remarkable that individuals undergoing hypernutrition (3500 kcal/day) return to physiological values of gonadotrophins when REE is normalized and largely before weight will come back to normal (Figure 6).

Frilessity (sensitivity to cold) and macrovascular syndrome such Raynaud’s phenomenon are frequently observed in women affected by hypothyroid hypoamennorhoea and testify to the impact of a low aREE on the thermogenesis and vasomotor reflex. The effect of decreased thermogenesis on

### Table II. Body composition and resting metabolic rate (RMR) at baseline (n = 20). Figures in parentheses are percentages

<table>
<thead>
<tr>
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<th>Mean ± SD</th>
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<tr>
<td>Fat mass (FM) (kg)</td>
<td>6.32 ± 3.55 (15.23 ± 7.89)</td>
</tr>
<tr>
<td>Lean mass (LM) (kg)</td>
<td>31.07 ± 3.14 (84.76 ± 7.89)</td>
</tr>
<tr>
<td>Total body water (TBW) (kg)</td>
<td>24.71 ± 1.84 (68.23 ± 8.63)</td>
</tr>
<tr>
<td>RMR (kcal/24 h)</td>
<td>927 ± 191</td>
</tr>
<tr>
<td>Predicted RMR (kcal/24 h)</td>
<td>1196 ± 80.45*</td>
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*Significant difference between RMR and predicted RMR \((P < 0.05)\).

### Table III. Mean ±SD of hormonal values at baseline

<table>
<thead>
<tr>
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<th>Anorexia nervosa (n = 20)</th>
<th>Control values (n = 18)</th>
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<tbody>
<tr>
<td>LH 0 (mIU/ml)</td>
<td>0.83 ± 0.97a</td>
<td>5.9 ± 2.5</td>
</tr>
<tr>
<td>S LH (mIU/ml)b</td>
<td>27.3 ± 33.58</td>
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</tr>
<tr>
<td>FSH 0 (mIU/ml)</td>
<td>3.2 ± 2.64a</td>
<td>6.5 ± 2.8</td>
</tr>
<tr>
<td>S FSH (mIU/ml)b</td>
<td>25.72 ± 19.07</td>
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<tr>
<td>Testosterone (ng/ml)</td>
<td>0.46 ± 0.14</td>
<td>0.4 ± 0.2</td>
</tr>
<tr>
<td>Free testosterone (%)</td>
<td>0.76 ± 0.24</td>
<td>0.9 ± 0.4</td>
</tr>
<tr>
<td>Androstenedione (ng/ml)</td>
<td>1.11 ± 0.55</td>
<td>1.5 ± 0.7</td>
</tr>
<tr>
<td>DHEAS (μg/ml)</td>
<td>2.24 ± 1.65</td>
<td>1.2 ± 0.8</td>
</tr>
<tr>
<td>SHBG (nmol/l)</td>
<td>100.74 ± 35.2a</td>
<td>52 ± 28</td>
</tr>
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LH = luteinizing hormone; FSH = follicle stimulating hormone; DHEAS = dihydroepiandrosterone sulphate; SHBG = sex hormone binding globulin.

Significant difference \((P < 0.0001)\) compared with control values.

bS LH and FSH represent the sum of LH and FSH plasma levels at T0, T15, T30, T60 min during a gonadotrophin-releasing hormone (GnRH) test (100 μg IV).
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\[ r = 0.616 \quad P < 0.0001 \]

Figure 5. Resting metabolic rate is correlated with luteinizing hormone (LH) response (sum of LH) to gonadotrophin-releasing hormone (GnRH) test, during refeeding of anorexia nervosa. Taken from Lefebvre et al. (1995).

Figure 6. Refeeding a woman with anorexia nervosa restores the resting metabolic rate (RMR) and the physiological response of luteinizing hormone (LH) and follicle stimulating hormone (FSH) to gonadotrophin-releasing hormone (GnRH) test (ΔLH), in spite of persistent underweight. Taken from Lefebvre et al. (1995).
hypothalamic blood flow and neurohormonal secretion is a realistic concept which may explain a large number of ovulatory and infertility disorders occurring in hyperactive and chronically food restricted women without apparent weight loss. In clinical practice, assessment of aREE compared with eREE appears to be a useful means of detecting hypometabolic ovulatory disorders and quantifying objectively the intensity of energy deficit (Figure 7).

Figure 7. Hypothetical mechanism of the nutritional regulation of ovulation.

Several candidates may be involved as links between nutritional status and cycle disorders: (i) alterations in metabolic fuels, mainly fatty acid and glucose; (ii) decrease in peripheral hormones such as insulin, IGF-I and leptin, all being able to modulate gonadotrophin secretion; (iii) dysfunction of neurohormonal regulation of gonadotrophin secretion; and (iv) reduction of basal metabolic rate and thermogenesis affecting hypothalamic secretion by changes in vascular flow and/or neurosecretion. Hormonal induction of ovulation has to be performed when women have re-established weight and food intakes compatible with pregnancy (Bringer et al., 1985).

Conclusion

Careful evaluation of eating attitudes, food intakes and exercise is a main step in investigating the possible causal factors involved in ovulatory disorders responsible for infertility. The data presented above suggest that the hypothalamic–pituitary–ovarian axis is extremely sensitive to relatively mild restrictions of calorie intake inducing a negative energy balance. Alterations in the composition of the diet may assist in disturbances of gonadal function. Another cofactor is the rapidity of weight loss. Many women undergoing heavy exercise experience relative eating insufficiency disorders.

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