Menstrual Disturbances in Athletes: A Focus on Luteal Phase Defects

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ABSTRACT

DE SOUZA, M. J. Menstrual Disturbances in Athletes: A Focus on Luteal Phase Defects. Med. Sci. Sports Exerc., Vol. 35, No. 9, pp. 1553–1563, 2003. Subtle menstrual disturbances that affect the largest proportion of physically active women and athletes include luteal phase defects (LPD). Disorders of the luteal phase, characterized by poor endometrial maturation as a result of inadequate progesterone (PG) production and short luteal phases, are associated with infertility and habitual spontaneous abortions. In recreational athletes, the 3-month sample prevalence and incidence rate of LPD and anovulatory menstrual cycles is 48% and 79%, respectively. A high proportion of active women present with LPD cycles in an intermittent and inconsistent manner. These LPD cycles are characterized by reduced follicle-stimulating hormone (FSH) during the luteal-follicular transition, a somewhat blunted luteinizing hormone surge, decreased early follicular phase estradiol excretion, and decreased luteal phase P4 excretion both with and without a shortened luteal phase. LPD cycles in active women are associated with a metabolic hormone profile indicative of a hypometabolic state that is similar to that observed in amenorrheic athletes but not as comprehensive or severe. These metabolic alterations include decreased serum total triiodothyronine (T3), leptin, and insulin levels. Bone mineral density in these women is apparently not reduced, provided an adequate estradiol environment is maintained despite decreased P4. The high prevalence of LPD warrants further investigation to assess health risks and preventive strategies. Key Words: EXERCISE, HYPOMETABOLIC STATE, ESTRADIOL, PROGESTERONE, LUTEAL PHASE DEFECTS

Menstrual disturbances associated with exercise are reported in active women and athletes who participate in physical activity ranging from recreational to strenuous exercise training. Amenorrhea, which involves complete follicular and luteal suppression, is the most severe menstrual disturbance experienced by athletes associated with virtually all sports and across a range of activity levels (24,40). The prevalence of amenorrhea has been reported to range from 1% to 44% among athletic women (24,40), with the highest prevalence observed in sports that emphasize a thin physique, like long-distance running and gymnastics (24,40). Less severe menstrual disturbances in active women and athletes include luteal phase defects (LPD), which affects the largest proportion of exercising women and is reported to be as high as 79% (9). This review will focus on the endocrine aspects of LPD in exercising women, although comparisons with various endocrine features of amenorrheic athletes will be referenced. Factors that may result in more severe forms of ovulatory dysfunction, such as anovulation and amenorrhea, which may also be associated with LPD, will be reviewed. The reader is directed to other recent reviews on factors associated with amenorrhea in athletes (24,40).

CLINICAL AND DIAGNOSTIC CHARACTERISTICS OF LUTEAL PHASE DEFECTS

The most important feature of the luteal phase of a menstrual cycle is the formation of a corpus luteum that develops from the cellular wall of a postovulatory follicle in response to a surge of luteinizing hormone (LH) (2,30). The most important function of the corpus luteum, in turn, is production of the ovarian steroid P4, which is essential for the secretory transformation of the endometrium and maintenance of early pregnancy (2,30). In women with a LPD, the ovarian system functions at a level good enough to ovulate, but that level is far from being adequate enough to support implantation (2,30). The lifespan of a corpus luteum is 14–16 d in a nonfertilized cycle and until the luteal-placental shift in a fertilized cycle (2,30). In clinical settings, LPD have also been referred to as luteal phase inadequacy and insufficiency to describe the coincident poor quality of the endometrium (2,30). Short luteal phases are actually a variant of a LPD used specifically to describe luteal phases of 10 d or less (35,36). Jones (17) originally described a LPD in 1949 as inadequate P4 production, either in volume or duration of output, which causes endometrial failure of blastocyst implantation and is present in multiple cycles. Clinically, the P4 inadequacy associated with LPD causes asynchronous follicular growth in the subsequent menstrual cycle, compromised oocyte maturation, and differentiated.
(out of phase) function of the endometrium. All of these factors are associated with low rates of cycle fecundity and high rates of embryonic loss, i.e., infertility and spontaneous abortion (2,30). LPD are predominately a product of a dysregulation in folliculogenesis, although other causes are suggested (2,19,30).

Clinical criteria for the diagnosis of LPD have historically been controversial but include an out of phase endometrial biopsy, abnormal basal body temperature patterns, and low urinary P4 levels (17,18). More recently, lively debate in the clinical forum has focused on the use of single and multiple serum or urinary measurements of P4, assessment of luteal phase length, ultrasound measurement of preovulatory follicle size, and timed endometrial biopsy (19,30). In research settings, the “gold standard” has been the costly and time-consuming daily measurements of P4 and LH in blood, urine, or saliva for multiple consecutive menstrual cycles (11,19,30). Providing detailed assessments of ovarian steroid levels across multiple cycles is necessary to accurately diagnose LPD in women, whether sedentary or active because these types of menstrual perturbations occur intermittently and inconsistently (19,30). Single menstrual cycle evaluations may result in LPD being missed or misclassified because their presentation is intermittent. In the body of exercise literature, most researchers have limited their menstrual cycle evaluations to a single cycle and have likely underestimated the occurrence of these events or misclassified the status of an individual (9).

Clinical consequences of LPD that have been established in sedentary women include infertility and spontaneous abortion, both due to the effects of an inadequate P4 environment (19,30). In athletes, the overall incidence of infertility remains unknown and warrants further study. Another clinical consequence of LPD that has been questioned is the effect of LPD on bone mineral density (BMD). This issue has been addressed both in sedentary women and in exercising women. Data reported by Prior et al. (32) suggested that LPD in a single cycle, more than one cycle and in anovulatory cycles resulted in progressively more spinal bone loss in moderate- and long-distance runners. There are, however, multiple methodological problems associated with the Prior et al. (32) data set. The limitations include the methods used to assess LPD (pooling of single blood samples, which is discussed in the “Prevalence” section), the use of computed quantitative tomography to assess BMD, and the confusing effect of combining estrogen deficient anovulatory cycles with LPD cycles, as it is well established that anovulatory estrogen deficient cycles may affect bone health. Since then, De Souza et al. (8) found that despite significantly reduced P4 levels in exercising women with LPD, BMD at the lumbar spine and femoral hip was comparable to ovulatory sedentary women, provided the estradiol status was adequately maintained during the cycle. De Souza et al. (8) did, however, observe a trend for lower early follicular phase estrogen levels. Very similar to De Souza et al. (8), Waller et al. (39) reported that LPD were also unassociated with a decrease in BMD measured four times over a 17.5-month period in a sedentary group of 53 women in the Women’s Health Reproductive Health Study. It would be appropriate to study a large group of LPD active women for several years to further characterize effects of LPD on BMD. Effects of LPD on endometrial and breast tissue are unknown and too warrant evaluation.

REPRODUCTIVE HORMONE CHARACTERISTICS OF LPD IN EXERCISING WOMEN

The most pronounced ovarian steroid perturbations in exercising women with LPD are observed during the luteal phase. Compared with sedentary women, ovulatory exercising women with LPD experience alterations in both the length of the luteal phase and the production of luteal phase P4. In the face of normal menstrual cycle lengths, short luteal phases of less than 10 d and reduced P4 production by as much as 50% were reported as early as 1979 by Shangold et al. (34) and by other investigators of athletic women since that time in single (5,26,33,45) and multiple cycle evaluations (9,12). Typical ovarian steroid patterns and luteal phase characteristics in recreational runners with LPD are shown in Figure 1. Concomitant with shortened luteal phases, follicular phase length is prolonged in exercising women with LPD, and early follicular (days 2–5) phase estrone conjugate (E1C) levels are significantly decreased in ovulatory and LPD exercising women compared with ovulatory sedentary women (9,45). This decrease persisted throughout the mid (days 6–12) follicular phase in the exercising women with LPD. It is noteworthy that even though De Souza et al. (9) observed estradiol suppression in ovulatory exercising women both with and without LPD, this suppression was most pronounced in the exercising women with LPD (Fig. 1). Winters et al. (45) also reported decreased early follicular phase E1C excretion during a single menstrual cycle in cyclic runners. Curiously, in the face of suppressed luteal P4 levels, mean estradiol secretion during the luteal phase is not suppressed in athletes with LPD (9,26), perhaps indicating that the corpus luteum production of P4 is more susceptible than that of estradiol production in response to a reduction in gonadotropin support to the ovary. Loucks et al. (26) failed to observe differences in luteal estradiol levels measured in daily urine samples from one cycle in cyclic athletes with LPD compared with cyclic nonathletes. De Souza et al. (9) also failed to observe differences in luteal estradiol levels measured in daily urine samples across three cycles in regularly menstruating runners who were LPD compared with ovulatory sedentary women.

The luteal-follicular transition represents a critical period during the menstrual cycle when follicle recruitment is initiated (7,15). Reduced pituitary follicle-stimulating hormone (FSH) release during the luteal-follicular transition in exercising women with LPD has also been identified (9). This reduction in FSH may act in concert with suppressed LH pulsatility to impair ovarian function in athletes (9). This finding is consistent with a description of a FSH deficiency in infertile women (7). A delay in the rise of FSH during the luteal-follicular transition period can significantly delay the
FIGURE 1—Top, Characteristic consecutive menstrual cycles in a consistently ovulatory exercising subject. Middle, Characteristic consecutive menstrual cycles in a consistently LPD exercising subject. Bottom, Characteristic consecutive menstrual cycles in an inconsistently ovulatory exercising woman. Daily urinary excretion is shown for E1C (nanogram per milligram of Cr) on the left y-axis and PdG (milligram per milligram of Cr) on the right y-axis. Data are plotted relative to the first day of menses. Note in subject X2, in the right panel, an LPD with normal luteal phase length but inadequate progesterone production and in subject X3 in both the left and right panels, short luteal phases and inadequate progesterone production (adapted and reprinted with permission from De Souza et al. (9); copyright 1998, The Endocrine Society).

recruitment and maturation of follicles (1,15), negatively affect GnRH pulse frequency (1,15) and the preceding LH surge (1,15), and is also consistent with the notion in the clinical literature that LPD are a product of a dysregulation in folliculogenesis (1,2,19,30). The report of a delay in the rise of FSH during the luteal-follicular transition by De

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Continuum of Menstrual Disturbances in Athletes

Ovulatory | Luteal Phase Defect | Anovulation | Oligomenorrhea | Amenorrhea

FIGURE 2—Continuum of reproductive disturbances, ranging from ovulatory cycles, subtle presentations of LPD, and anovulatory cycles to the most severe menstrual disturbance, amenorrhea. Physically active women and athletes fluctuate between ovulatory cycles and LPD and anovulatory disturbances frequently. It also seems probable that amenorrheic athletes may experience LPD during recovery from amenorrhea.

Souza et al. (9) is suggestive of suppressed folliculogenesis in all exercising women, but is more pronounced in exercising women with LPD, and thus may contribute to infertility in this population. Although folliculogenesis may be compromised with LPD, to date, no evidence of a decreased preovulatory estradiol peak preceding the LH surge has been observed in exercising women (9). However, the day of the preovulatory estradiol peak occurred much later when compared with ovulatory sedentary and exercising women without LPD, consistent with prolonged follicular phases that occur in concert with short luteal phases (9).

Consistent with a reduction in gonadotropin support to the ovary, LH pulsatility is suppressed in exercise-associated LPD (26). In cyclic athletes with LPD, Loucks et al. (26) observed reduced LH pulses that were less frequent with larger amplitudes in cyclic athletes compared with high-frequency, low-amplitude LH pulses observed in sedentary regularly menstruating women. This pattern of LH pulsatility in LPD athletes is drastically different from that observed in amenorrheic athletes who displayed prepubertal LH pulse patterns (few pulses that appeared irregularly) (26). There is some evidence that the peak concentration of the LH surge itself may be blunted in women with LPD. LPD in 63 normally cycling infertile women were associated with smaller dominant follicles and a lower mid-cycle ovulatory LH surge compared with women without evidence of a LPD (1). In the study by De Souza et al. (9), a progressive decline in peak LH concentration was observed in the exercising groups as the type of menstrual disturbances progressed in severity from ovulatory cycles to LPD and anovulatory cycles. Many of the aforementioned ovarian and gonadotropin abnormalities have been linked to infertility in nonexercising women with LPD (1,2,18,19,30).

PREVALENCE OF LUTEAL PHASE DEFECTS IN EXERCISING WOMEN

The incidence of LPD in nonactive women is controversial, but estimates vary from 2% to 5% in normal ovulatory women and 3% to 20% in women with infertility (2,19). LPD occurs in athletes at a much greater prevalence than in nonactive women, representing the most common menstrual cycle abnormality associated with exercise (9): A 3-month sample prevalence and incidence rate of LPD and anovulatory cycles of 48% and 79%, respectively, has been reported in recreational athletes (9). Menstrual cycle disturbances in athletes and active women have been previously described as existing along a continuum of reproductive disturbances, ranging from subtle presentations of LPD and anovulatory cycles to the most severe presentation, amenorrhea (see Fig. 2). Due to the unobtrusiveness of these abnormalities, LPD in athletes and active women go undiagnosed. LPD present without any change in menstrual cycle length, and although these athletes continue to ovulate, some do so much later than the typical mid-cycle day 12-14 in “normal” ovulatory cycles. Ovulation can occur as late as day 20, 21, or even later in these athletes.

In 1979, Shangold et al. (34) published the first prospective observational case study to document the decreased P₄ production and a gradual shortening of the luteal phase in a woman during exercise training for a marathon. In that study, a clear inverse relationship between increased running volume and luteal phase length was observed. The concept that perturbations of the luteal phase and consequently, amenorrhea, were most often observed in athletes participating in strenuous or high volumes of exercise training became a common assumption. However, over the past few years, it has been clearly established that perturbations of the luteal phase can occur in many active women, including those participating in only recreational volumes (running 32 km-wk⁻¹ or 3 h-exercise-wk⁻¹) of exercise training, i.e., high-volume or strenuous exercise training is not a prerequisite for menstrual perturbations (9). In some of the cross-sectional studies limited to single menstrual cycle evaluations, investigators have similarly reported the occurrence of LPD in runners of varying activity levels (5,45). Broocks et al. (5), who assessed daily estradiol and P₄ levels, observed LPD in 7 of 17 recreational joggers who ran 30-45 km-wk⁻¹. Winters et al. (45) measured E1C and pregnanediol glucuronide (PDG) in daily urine samples and reported that 4 of 10 high-volume runners (106 km-wk⁻¹) and 5 of 10 joggers (30 km-wk⁻¹) displayed LPD. Schweiger et al. (33) also measured daily sex steroids and reported that 26 of 53 women who exercised a minimum of 3 h-wk⁻¹ (and some who practiced intermittent dieting) had either inadequate or short luteal phases.

Few studies have been completed that have evaluated multiple menstrual cycles in exercising women. Ellison and Lager (12) measured daily salivary P₄ levels in 15 cycles
from eight exercising women running 30 km-wk\(^{-1}\) with normal cycle lengths of 28 d, and observed significantly lower luteal P\(_4\) levels when compared with 19 cycles for nine women in a sedentary control group. Prior et al. (32) attempted a prospective evaluation of menstrual status in 66 moderate- and long-distance runners by measuring P\(_4\) in a "pooled" blood sample at the beginning and end of a 12-month period by combining (pooling) a single blood sample collected during the follicular phase with another collected during the luteal phase. This method is not representative of menstrual status and inadequate to detect a LPD. De Souza et al. (9) subsequently reported the prevalence and incidence of LPD in active women by measuring E1C and PdG in daily urine samples during three consecutive menstrual cycles in asymptomatic, regularly menstruating, moderately active women (compared with sedentary women). They observed a 3-month sample prevalence and incidence rate of LPD and anovulatory cycles of 48% and 79%, respectively, in 24 recreational-level joggers (32 km wk\(^{-1}\)). Despite the fact that all of the women in the study had consistent and repeatable menstrual cycle lengths of 27 d, almost half (46%) of the exercising women had inconsistent menstrual status from cycle to cycle; that is, intermittent presentations of ovulatory, LPD, and anovulatory cycles. In contrast, 100% of the sedentary women had consistent menstrual status presentations from cycle to cycle.

The observations in the De Souza et al. (9) study document several important findings. First, multi-cycle data confirm the findings of earlier single cycle cross-sectional observations of LPD in active women and athletes and confirm that active women, including those that ovulate, experience ovarian suppression, although at a much greater prevalence than that observed in single cycle studies (9). Second, menstrual cycle length is not an accurate marker of ovarian function in exercising women because a remarkably high incidence of LPD and anovulatory cycles and inconsistent menstrual status from cycle to cycle were reported in women with normal and repeatable menstrual cycle lengths (9). Third, because abnormal ovarian function (LPD and anovulation) was displayed by 33% of the exercising women consistently and another 46% inconsistently, previous investigators who evaluated only a single menstrual cycle and failed to see a disturbance may have underestimated the presence of these events if they made wider reference to overall menstrual status. Based on the De Souza et al. (9) data, a 38% underestimation of the 3-month sample incidence of LPD among regularly menstruating athletes may result. Therefore, if classification of menstrual status is based on only a single menstrual cycle evaluation in athletes and active women, then overall menstrual status may be misclassified, and only single cycle status can be discussed in those instances. Taken together, these data extend our understanding of the widespread frequency of LPD and ovulatory disturbances that occur in entirely asymptomatic physically active women of all activity levels with regular and consistent menstrual cycle lengths of 26–32 d. The high prevalence of these events warrants further study to assess health risks, including infertility, as the prevalence of infertility remains unknown in athletes but is likely to be greater than suspected. Because the presentation of these menstrual disturbances is irregular, it may be that the nature of the infertility associated is also episodic, but certainly documentation of this hypothesis is an important avenue of future investigative pursuit.

**DETECTION AND DEFINITION OF LUTEAL PHASE DEFECTS IN EXERCISING WOMEN**

Having defined the prevalence and importance of LPD in active women, consideration of the various strategies for documenting LPD in exercise studies is critical. Several issues deserve attention. Duration of luteal phase length is made by determining the interval between ovulation and menses where ovulation is assessed by the LH surge. The use of basal body temperature alone to determine the day of ovulation is inferior to the documentation of an LH surge (19,29). The criterion of a "short" luteal phase has been inconsistently presented in the infertility literature and has ranged from 9 to 11 d (2,19,22,35,36). Sherman and Korenman (35) and Strott et al. (36) originally defined a luteal phase of <10 d as "short," as both low peak levels of P\(_4\) and decreased follicular FSH were observed in association with this shortened luteal phase length. In the exercise literature, variable criteria have been utilized but have included the use of that originally presented by Sherman and Korenman (35) and Strott et al. (36); De Souza et al. (9,10) used <10 d and Beits et al. (3) used ≤9 d, which is the same as <10 d. In sedentary women, Waller et al. (39) also utilized <10 d as the criterion for a short luteal phase. Others in the exercise literature, however, have failed to use this criterion or failed to define a criterion (3,4,6,41). In future studies of menstrual function, it may be appropriate for exercise scientists to use a <10 d criterion to define a luteal phase as short, because this is consistent with that suggested in the clinical literature. It is important to recognize that short luteal phases alone (without reduced P\(_4\)) are not consistently linked to infertility in the clinical literature (19,30) and, therefore, should not be considered a sensitive diagnostic criterion for a LPD. Used alone or in combination with luteal phase length, the determination of daily P\(_4\) levels for at least one cycle, but preferably multiple cycles, has been recommended as the "gold standard" for the diagnosis of LPD in a research setting (18,19,30). The use of single serum daily measurements, however, is limited because daily blood sampling is overly invasive. Additionally, because P\(_4\) is secreted in a pulsatile manner, significant variability in the range of 5–15 ng·mL\(^{-1}\) of mid-luteal serum values for LPD have been reported (19). Less invasive strategies than daily blood draws for measuring P\(_4\) levels in a research setting can be accomplished using daily collections of urine or saliva. Investigators in the exercise literature have utilized these methodologies, but there is a lack of defined criteria to categorize cycles as LPD. De Souza et al. (9,10) measured PdG in daily urine samples for three menstrual cycles and reported the mean 3-d sum of mid-luteal PdG excretion to be 10.9 ± 1.2 mg·mg\(^{-1}\)·Cr\(^{-1}\) in LPD.
cycles versus 21.7 ± 1.4 and 17.8 ± 2.3 mg·mg⁻¹·Cr⁻¹ in ovulatory sedentary and exercising women, respectively. Other investigators have also described reduced daily urinary levels of P₄ in athletes and nonathletes (3,29,39,41,45), but a specific criterion for an inadequate luteal phase remains undefined. Perhaps a critical 3- or 5-d mid-luteal sum of P₄ measured in daily urine samples or a defined ratio increase above baseline levels may be appropriate. Future work should include an effort to adopt a standardized criterion for LPD in urinary (and salivary) assessments of P₄. Along these lines, McConnell et al. (29) have recently reported on the validity of ovulation detection algorithms using daily urinary steroid levels in female athletes.

LPD IN PROSPECTIVE EXERCISE TRAINING STUDIES

LPD have been induced by a few well-designed and controlled prospective exercise training studies in both women and nonhuman primates. Bullen et al. (6) exercise trained sedentary women for two menstrual cycles, after monitoring one control cycle. The women were randomly assigned to either a weight maintenance or a weight loss group and exercise was abruptly initiated up to a volume of 16.1 km·d⁻¹. Although the initial report detailed a high incidence of LPD and delayed menses, Beitins et al. (3) performed an in-depth reanalysis of the Bullen et al. (6) data that focused solely on the LPD. They reported that of the 28 women, 18 had either a short or inadequate luteal phase, and LPD presented in 38% of the total 53 cycles studied. Among the LPD cycles, 30% had normal luteal phase lengths (13–14 d) but had inadequate P₄ production, and 70% had short luteal phases of 6 d (see Fig. 3). It was concluded that the initiation of strenuous exercise training can cause LPD in two primary forms: 1) an inadequate form, when P₄ production is low in the face of luteal phase lengths of ≥ 9 d; and 2) a short form, when, in conjunction with low luteal P₄, luteal phase lengths of < 9 d occurred. This latter presentation was categorized as the more severe LPD (3). In another almost identical 2-month exercise training study, Williams et al. (41) limited exercise to either the follicular or the luteal phase in two different groups of women and similarly evaluated daily sex steroid excretion. Of the 19 exercise training menstrual cycles monitored, 45% were characterized as LPD, whereas none of the 18 menstrual cycles monitored in the control group demonstrated any form of an LPD. The overall incidence of LPD initiated by the exercise training in this study was 42%, which is similar to the 38% incidence of LPD in the study of Bullen et al. (6). It was concluded that abruptly increasing exercise results in LPD in previously sedentary women and that corpus luteum
perturbations are independent of the menstrual phase in which exercise was initiated.

It is also important to discuss the nonhuman primate exercise training studies recently published by Williams et al. (42,43) because LPD were observed in the cycles immediately preceding a transition from ovulatory cycles to amenorrhea. This group (42,43) demonstrated both the induction and reversal of amenorrhea during prospective exercise training utilizing a monkey model where reproductive hormones were measured in blood. In eight monkeys, food intake was maintained at a constant level while daily running distance was gradually increased to 12.3 km·d⁻¹. Amenorrhea was induced with no change in body weight after 14.3 months of training. In the cycle before the transition to amenorrhea, there was a significant reduction of 34% in serum P₄ and a significant decrease in LH, consistent with that observed in menstrual cycles classified as LPD and in the case of three monkeys, anovulatory (see Fig. 4). When comparing the P₄ levels in the two menstrual cycles immediately preceding the amenorrhea, levels decreased from 8.3 ± 1.9 ng·mL⁻¹ two cycles before the amenorrhea to less than 50% of that level (3.8 ± 0.7 ng·mL⁻¹) in the cycle immediately before amenorrhea. Although overall menstrual cycle and follicular phase length increased in the cycle immediately preceding the amenorrhea, luteal phase length was not shortened in five of eight monkeys that ovulated. Without moderating the volume or intensity of the exercise regime, Williams et al. (42) was successful in reversing the amenorrhea over a range of 12–57 d in four monkeys by supplementing their energy intake by 58%. Body weight significantly increased, and menses returned in all four monkeys. In the menstrual cycle immediately preceding the first post LH surge cycle, P₄ increased from 0.24 ± 0.09 ng·mL⁻¹ during late amenorrhea to 5.17 ± 0.5 ng·mL⁻¹. These P₄ levels are also consistent with reproductive hormones, period, and consistent with ovulatory levels, but they are still below that of the luteal phase during the first of the two cycles immediately preceding amenorrhea, (8.3 ± 1.9 ng·mL⁻¹), which were also ovulatory (42). These data presumably suggest that during the transition from ovulatory cycles to amenorrhea, LPD and anovulatory cycles in the form of inadequate P₄ production, lengthening of the follicular phase, and decreased LH are apparent and that LPD also occur during the transition back to ovulatory cycles from amenorrhea in these monkeys. These data are also consistent with the exercise training studies of Bullen et al. (6) and Williams et al. (41) previously discussed. However, because both Bullen et al. (6) and Williams et al. (41) only trained their subjects for two menstrual cycles, it is unclear whether they would have progressed to develop amenorrhea over a longer training period. It appears that LPD and anovulatory become apparent in models of exercise training where the exercise regime is gradual and prolonged (42,43), or abrupt (6,41). During the transition from ovulatory cycles to amenorrhea, it appears that LPD and anovulatory cycles are likely and that LPD also occur during the transition back to ovulatory cycles from amenorrhea (see Figs. 3 and 5).

**FIGURE 4**—Effects of training on plasma levels of reproductive hormones in the group of exercising monkeys (N = 8) during two cycles (cycle 2 and cycle 1) preceding onset of amenorrhea for three 30-d periods (AM1, AM2, and AM3). *Significant difference P < 0.05 compared with sedentary monkeys; †significant difference P < 0.05 compared with corresponding time point in the sedentary control group of monkeys (adapted and reprinted with permission from Williams et al. (42); copyright 2001, The Endocrine Society).

**METABOLIC HORMONES IN EXERCISING WOMEN WITH LUTEAL PHASE DEFECTS**

It is believed that during times of chronic energy deficiency, a shift in metabolic fuels occurs that rehypertensions energy away from the costly processes of reproduction and toward the essential processes of cellular, locomotive, and other life-sustaining metabolic functions (38). With respect to exercising women, eloquent short-term experiments (25,28,44) manipulating both dietary intake and energy ex-

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FIGURE 5—The metabolic and reproductive hormone perturbations that have been identified to date and associated with exercise and menstrual status, including eumenorrheic ovulatory cycles, LPD cycles and amenorrhea. All values are depicted by arrows signifying the magnitude of the alteration reported. The proposed relationship to menstrual status is also shown. The repeated transitions from ovulatory cycles and LPD cycles are shown and transitions during recovery from amenorrhea where an individual is likely to experience LPD cycles.

Metabolic Hormones and Substrates Relative to Sedentary Women

- Total T₃
- Leptin
  - Insulin
  - Growth Hormone
  - IGF-1/IGFBP-1
- Cortisol
- Glucose

Reproductive Hormones Relative to Sedentary Women

- LH Pulsatility
- FSH
- Estradiol
- Progesterone

penditure have revealed a tight correlation between energy availability and the modulation of the GnRH pulse generator. Support for a causal relationship between energy availability and menstrual cyclicity was recently provided by Williams et al. (42,43). The observation that circulating T₃ (a marker of energy balance) was correlated with both the induction and reversal of amenorrhea lends support to the idea that the suppression of reproductive function was linked with adaptive mechanisms to reduce energy expenditure (43). Although no prospective studies in humans have demonstrated a correlation with energy conserving processes and the induction of amenorrhea, several previous cross-sectional studies demonstrated that amenorrheic athletes exhibit hormonal profiles resembling those found with chronic caloric restriction, i.e., a hypometabolic state (see Fig. 5) (20,21,26,27).

Recently, researchers have demonstrated that there are indications of a similar metabolic paradigm of an energy adaptation and low energy availability in athletes with LPD (10). In a follow-up to an earlier study, De Souza et al. (10) have recently investigated whether a hypometabolic pattern of hormones is found in exercising women classified as ovulatory or LPD by daily urinary levels of ovarian steroids for three menstrual cycles and compared them with sedentary ovulatory women. Blood samples were collected during each follicular phase for the measurement of metabolic hormones. Both groups of the exercising women exhibited a decrease in total T₃, a classic sign of a reduced metabolic rate (10). The low T₃ syndrome observed in the LPD runners was similar in magnitude to that reported in amenorrheic athletes and in cyclic ovulatory runners who had LPD by Loucks et al. (26). Other hormone changes consistent with a hypometabolic state that were observed in exercising women with LPD include lower leptin and insulin levels (10). Both insulin and leptin were also observed to be lower in the exercising women with LPD compared with both the sedentary and exercising ovulatory women in the study by De Souza et al. (10). Not only were leptin levels suppressed in the exercising LPD group but also in the exercising ovulatory women, similar to that observed for total T₃. Laughlin and Yen (20,21) reported a relative hypoinsulinemia in amenorrheic versus cyclic athletes and reduced 24-h levels of leptin in both cyclic and amenorrheic athletes compared with sedentary women. Loucks et al. (28) have also demonstrated that an acute exposure to a combined regime of exercise training and caloric restriction significantly reduced circulating insulin levels. It appears that exercising women with LPD, in the face of normal menstrual cycle lengths, present with decreased insulin and leptin, but the extent of the disturbance is not as severe as that observed in amenorrheic athletes but distinguishes this group from the cyclic ovulatory exercising women (10). And because exercising ovulatory women with LPD experience intermittent changes in their menstrual status, intermittent changes are probable in their metabolic status that occur as an energy conserving adaptation that is likely first
defined by changes in circulating T₃ (10,25,28,44). These findings are suggestive of a compromised metabolic state presumably indicating that unfavorable combinations of dietary intake and physical exercise lead to a dysregulated corpus luteum.

Because it has been established that even moderate weight loss of 1 kg per month is associated with decreased P₄, even in women of normal weight (11,33), it is noteworthy that the exercising women in the De Souza et al. (9,10) studies did not exhibit any change in body weight across the three menstrual cycle period and did not weigh less than the sedentary control group. There are several examples of exercise-associated perturbations in menstrual function that are not accompanied by significant weight loss (12,42,43). Most notably, Williams et al. (42,43) demonstrated that during exercise training in monkeys, the transition from ovulatory cycles to amenorrhea was not associated with weight loss but rather a significant decrease in resting T₃, presumably indicating a decrease in energy expenditure (i.e., energy conservation) to restore energy balance. Similar to the Williams et al. (42,43) studies, the metabolic stress of the presumptive intermittent short-term negative energy balance was not obvious when examining body weight in the De Souza et al. (10) study but rather was manifested by its impact on metabolic hormones and subsequently on luteal function in response to the presumed energy adaptation (6,10,42,43). It is likely that the exercising women in the studies by De Souza et al. (9,10) are not unlike the vast majority of exercising women who practice moderate dietary restriction, perhaps with high levels of cognitive restraint (37), in their efforts to attain targeted health and fitness goals or a specific body image. These women probably experience ongoing and varying degrees of energetic stress that affect their metabolic and reproductive status.

LESSONS LEARNED FROM OVARIAN SUPPRESSION IN NON-WESTERN SOCIETIES

Ovarian suppression, as assessed by salivary progesterone levels in non-Western communities in association with chronic energy deficiency related to poor environmental conditions, is discussed to present yet another demonstration of adaptive strategies to energetic stress. These data reinforce the concept that the suppression of reproductive function is likely an adaptive energy response to environmental conditions of energetic stress and provide a natural example of the impact of LPD on fertility. Ellison and colleagues (11-14,16,23,31) have described ovarian suppression of salivary P₄ in nontraditional subsistence and hunter-gatherer communities from different continents with varying ecologies and environmental conditions (see Fig. 6). These communities are exposed to seasonal changes in food availability and subsistence work. In addition, suppression of P₄ has been observed in saliva (12,23) and urine (5,9,26,45) in Western groups of runners.

The Lese of the Ituri Forest in Zaire of Central Africa are subsistence farmers who practice exhausting slash-and-burn horticulture and are frequently exposed to involuntary shortages in food availability during which time weight loss is observed (11,13,14). As indicated by suppressed salivary P₄ in samples collected twice weekly for 4 months, ovulatory frequency is drastically reduced to 56%. Moreover, the observed P₄ levels in the Lese are lower than that observed in the runners and the sedentary controls from the Boston studies of Ellison and colleagues (11,12,23). These data suggest that P₄ levels and ovarian function vary during periods of decreased food availability imposed involuntarily and is associated with weight loss (0.95 kg) thus creating a negative energy balance and presumably plays a role in the low fertility rates observed in this region. A similar example of energetic stress is observed in the Tamang women from the central highlands of Nepal (31), except this example is more reflective of extreme volumes of involuntary energy expenditure. This society subsists on agriculture and is subject to very heavy physical workloads with travel between the Himalayan foothills and long hours spent transplanting rice during the summer monsoons (11,31). Food availability is not as great an issue among the Tamang (11,31). Saliva samples were collected every other day during the winter and during the more physically demanding summer monsoon in these women. Salivary P₄ levels were suppressed during the summer monsoons when an average weight loss of 0.99 kg occurred, and again P₄ levels were lower than that observed in the Boston samples of women (11,12,23). Ovulatory frequency was only 38% during the summer monsoon season, compared with 56% in the Lese women. Jasienska and Ellison (16) have shown similarly suppressed salivary P₄ levels in Polish farm workers who perform a high amount of manual labor. Thus, ovarian suppression and LPD contribute to low cycle fecundity and is primarily the result of a negative energy balance created by high levels of involuntary energy expenditure in these two populations.

The different baseline levels, but similar patterns, of P₄ in these various groups reveal a paradigm of ovarian function in different populations from different geographical regions with different local ecological influences and is eloquently depicted by Ellison (11) in Figure 6. As Ellison (11) has pointed out, in situations where energy deficiency results, whether from voluntary food restriction and voluntary en-
nergy expenditure, as observed in traditional groups of Western women like the Boston samples (12,23), or whether from decreased food availability and subsistence-related energy expenditure, as observed in nontraditional subsistence farmers and foraging communities in Zaire, Nepal, and Poland (11,13,14,16,31), ovarian function is suppressed, as reflected by reduced P4 levels, and low cycle fecundity in a qualitatively similar manner. Interestingly, the luteal suppression observed in the non-Western communities of women presents as more quantitatively severe than in Western women as their overall levels of P4 are much lower (11) (see Fig. 6). In situations where the local ecology of a geographic region causes an energetic stress that reduces energy availability unassociated with self-imposed restrictive eating or exercise, i.e., involuntary behaviors, luteal suppression is a common adaptive response to conserve energy during the time period of limited energy availability. This paradigm is similar to the luteal suppression and LPD that is observed in Western groups of exercising women (10,12) and the energetic stress associated with the prospective training studies in humans and nonhuman primates (6,42,43). It is also of interest that LPD and anovulatory cycles have also been observed in Western women who practice cognitive dietary restraint (37).

SUMMARY, CONCLUSIONS, AND RECOMMENDATIONS

Exercising women who exhibit mild to moderate menstrual cycle abnormalities revert back and forth from ovulatory cycles, LPD cycles, and anovulation rather frequently, and this is probably mediated by changes in energy availability that result in an energy adaptation to conserve fuel (10,11,20,38). The possibility that the same woman may express many of these disturbances intermittently may be more common than previously realized (9). It is therefore probable that exercising women with LPD are in a state of an intermittent short-term negative energy balance and are likely adapting to unfavorable combinations of dietary intake and physical exercise that lead to an energy adaptation, including altered metabolic hormones and then, consequently, compromised luteal function (10). A similar adaptive energetic paradigm is observed in non-Western communities of women who also experience suppressed ovarian function in the face of limited energy availability (11–14,16,23,31). LPD may serve as an antecedent to amenorrhea in athletes and athletes may also experience LPD during recovery from amenorrhea. The clinical consequences of LPD in athletes warrant further investigation but presumably include infertility and spontaneous habitual abortion. Bone health is apparently not compromised in women with LPD, but careful examination of follicular estradiol over time and subsequent impact on bone warrants further investigation (8,39). Careful consideration should be given to standardizing the methods of classifying LPD. Future research should evaluate the clinical consequences of LPD in athletes and continue to examine the interrelationships of eating behaviors and stress, caloric intake, bone health, and menstrual cycle physiology.

REFERENCES


