Effects of age on the irregularity of LH and FSH serum concentrations in women and men

STEVEN M. PINCUS, JOHANNES D. VELDHUIS, THOMAS MULLIGAN, ALI IRANMANESH, AND WILLIAM S. EVANS

Department of Internal Medicine and National Science Foundation Center for Biological Timing, University of Virginia, Charlottesville 22908; Medical College of Virginia, Richmond 23249; and Endocrine Section, Veterans Affairs Medical Center, Salem, Virginia 24153

Pincus, Steven M., J ohannes D. Veldhuis, Thomas Mulligan, Ali Iranmanesh, and William S. Evans. Effects of age on the irregularity of LH and FSH serum concentrations in women and men. Am. J. Physiol. 273 (Endocrinol. Metab. 36): E989–E995, 1997.—We evaluated an apparent distinction between follicle-stimulating hormone (FSH) and luteinizing hormone (LH) dynamics: visually, it appears that the pattern of serum concentrations of FSH is more irregular than that of LH in younger human females. We studied healthy humans, with LH and FSH serum samples obtained every 10 min for 24 h. Three groups were studied: 24 young females (8 early follicular (EFol), 8 late follicular (LFol), and 8 midluteal (MLut)); 8 postmenopausal females; and 17 males 21–79 yr of age. To quantify serial irregularity, we utilized approximate entropy (ApEn), a scale- and model-independent statistic. For young females, FSH was consistently more irregular than LH per subject: among the younger subjects, ApEn(FSH) > ApEn(LH) = 0.342 ± 0.270; ApEn(FSH) > ApEn(LH), P < 0.00001; ApEn(FSH) > ApEn(LH) for 23 of 24 subjects. For each cycle stage, pairwise ApEn(FSH) > ApEn(LH): P < 0.005 for both LFol and MLut, P < 0.01 for EFol. Notably, for the postmenopausal women, the irregularity difference vanished: ApEn(FSH) = ApEn(LH) = 0.008 ± 0.205. Males exhibited qualitatively similar results: ApEn(FSH) – ApEn(LH) was significantly and negatively correlated with age (r = −0.75, P = 0.0006). The capability to quantify the extent of differences between FSH and LH release, beyond the general 1:1 correspondence between primary LH and FSH pulses, suggests a means to assess bimodal changes as a clinical marker of altered reproductive status in a variety of settings, e.g., a perimenopausal milieu. Mechanistically, the erosion of unequal FSH-LH regularity with age is consistent with a loss of synchrony control within the integrated hypothalamo-pituitary-gonadal axis.

greater understanding of the evolution of the gonadotropin-releasing hormone (GnRH)-luteinizing hormone (LH)-follicle-stimulating hormone (FSH) axis with aging is of vital importance both scientifically, in understanding the physiology of reproductive capacity, and clinically, in treating disorders of fecundity and fertility. Herein, we assess one aspect of this axis via study of the joint LH and FSH serum concentration time series. In particular, we attempt to determine the validity and scope of an apparent distinction between FSH and LH dynamics in blood: visually, it appears that the pattern of serum concentrations of FSH is more irregular than that of LH, with many more minor episodes or subordinate activity (to primary pulses) in younger human females. As a suitable analytic strategy to quantify potential irregularity distinctions, we employ approximate entropy (ApEn) (13, 20), described in METHODS. We study younger females in three distinct menstrual cycle stages to ascertain the consistency of this hypothesis; postmenopausal females, to determine whether this finding persists in the older female; and males across a spectrum of ages, to determine possible parallelism to corresponding findings for the female.

This study is motivated by recent significant LH-FSH distinctions in sheep (11), seen both vividly as secreted, i.e., as measured from hypophyseal portal blood (HPB), and somewhat less evidently measured in peripheral blood. The rationale for considering differences between FSH and LH dynamics stems from multiple studies of these two hormones supporting the notion of general (albeit imperfect) concordance between the episodic release of LH and FSH, incorporating both the very initial studies assessing the pulsatile nature of LH release (10, 22) and more recent studies using animal (7) and human (2, 3, 21, 30, 31) models. Thus ascertaining subordinate LH-FSH differences beyond a general 1:1 correspondence between primary LH and FSH pulses may obliquely mark degrees of feedback, control, or varying external inputs into the coupled system. Most importantly, quantitative changes in these (FSH-LH) differences may unveil corresponding underlying mechanistic physiological changes of potential clinical consequence.

METHODS

Twenty-four healthy young premenopausal women (mean age 27 yr; range 19–38 yr) and eight healthy postmenopausal women (mean age 59 yr; range 50–70 yr) were studied at the University of Virginia General Clinical Research Center (GCRC). The premenopausal women were further segmented by subgroups: early follicular phase (days 2–5 of menses; n = 8), late follicular phase (1–4 days before ovulation; n = 8), and midluteal phase (days 5–8 after ovulation; n = 8) of subjects' menstrual cycles. In this premenopausal group, ovulation was presumed to have occurred during the study cycle when the development of a normal preovulatory follicle was followed by its disappearance, as documented with transvaginal ovarian ultrasonography. All older women had experienced menopause ≥1 yr before the study and were admitted only after discontinuing any hormone replacement ≥6 wk earlier. Morbidly obese women were excluded from the study; ~80% of all subjects were within 20% of their ideal body weight. Only one subject of the entire group gave a positive history for smoking.

Seventeen healthy nonsmoking men within 20% of ideal body weight (mean age 47 yr; range 21–79 yr) were studied at
the Veterans Affairs Medical Center, Salem, VA, and the GCRC, University of Virginia.

For both male and female studies, 1 h after placement of an indwelling heparin cannula into a forearm vein, blood samples were obtained beginning at 0800 clocktime at 10-min intervals for 24 h (n = 144 points/subject). On the day of sampling, subjects were provided breakfast, lunch, and dinner, and water was allowed ad libitum. The participants refrained from daytime naps and were allowed to sleep at night. Serum FSH and LH concentrations were measured in duplicate robotically by two-site monoclonal immunoradiometric assays provided by Nichols Laboratories (San Juan Capistrano, CA) as previously described (26, 32). The FSH and LH standards were, respectively, the Second and First International Reference Preparations. Dose-dependent within-assay coefficients of variation ranged from 3 to 13%. Further subject and assay descriptions have been given earlier (1, 26, 32).

Quantification of episodicity. To quantify irregularity, we utilize ApEn, a model-independent statistic defined in Ref. 13, with further mathematical properties given in Refs. 17, 18, and 20. ApEn is complementary to pulse detection algorithms widely employed to evaluate hormone secretion time series. ApEn evaluates both dominant and subordinant patterns in data; notably, it will detect changes in underlying episodic behavior that do not reflect peak occurrences or amplitudes, a point that is germane to the present analysis. Additionally, ApEn provides a direct barometer of feedback system change in many coupled systems (14). Among representative endocrine applications, in pathophysiology, ApEn has shown vivid distinctions (P < 10^{-10}) between normal and tumor-bearing subjects for GH (5) and ACTH (27), as well as a pronounced and consistent gender difference in GH irregularity in both humans and rats (16).

ApEn assigns a nonnegative number to a time series, with larger values corresponding to greater apparent process randomness (serial irregularity) and smaller values corresponding to instances of more recognizable patterns or features in the data. Two input parameters, m and r, must be specified to compute ApEn. Briefly, ApEn measures the logarithmic likelihood that runs of patterns that are close (within r) for m contiguous observations remain close (within the same tolerance width r) on next incremental comparisons; the precise mathematical definition is given in Ref. 13.

For this study, we calculated ApEn values for all data sets, m = 1 and r = 20% of the SD of the individual subject time series. Normalizing r to each time series SD gives ApEn a translation and scale invariance to absolute serum concentration levels (15). Previous studies that included both theoretical analysis (13, 17) and clinical applications (5, 15, 16, 19, 27) have demonstrated that the input parameters indicated above produce good statistical validity (reproducibility) for ApEn for time series of the lengths considered herein (n = 60–300 data points).

The statistical comparisons below for discrimination between paired (LH and FSH) values employed the paired t-test with unknown variance and the nonparametric Wilcoxon signed-rank test. The application of both these complementary statistical techniques was chosen to ensure robustness of the results to a range of distributional assumptions.

RESULTS

Young females. Representative young female LH and FSH serum concentration time series are shown in Fig. 1, A and B (midluteal phase) and C and D (late follicular phase). Table 1 indicates the mean level and ApEn values for each of LH and FSH, and ApEn(LH) – ApEn(FSH), for younger females, both combined (pooled) and by menstrual cycle phase, as well as for older females. The individual younger subjects’ ApEn(FSH) – ApEn(LH) values are shown in Fig. 2 (left).

When the three young female groups are combined, 23 of 24 subjects showed a positive ApEn(FSH) – ApEn(LH) value, establishing a consistency across cycle stage to the hypothesis that FSH serum concentrations are more irregular than LH concentrations per subject. For the combined younger group, ApEn(FSH) > ApEn(LH), P < 0.00001 for both paired t- and signed-rank tests. By subgroup phase, ApEn(FSH) > ApEn(LH): early follicular, P < 0.01, signed-rank test and P < 0.04, paired t-test; late follicular, P < 0.005, signed-rank test and P < 0.008, paired t-test; midluteal, P < 0.005, signed-rank test and P < 0.0006, paired t-test.

There were also individual cycle phase differences between individual subject mean serum concentrations of LH and FSH. By subgroup, mean FSH levels were higher than mean LH levels in both the early follicular phase, P < 0.01, signed-rank test and P < 0.005, paired t-test, and in the midluteal phase, P < 0.04, signed-rank test and P < 0.12, paired t-test. In contrast, for the late follicular phase, mean LH levels were higher than mean FSH levels, P < 0.02, signed-rank test and P < 0.06, paired t-test. Overall, for the combined younger group, mean LH and FSH levels did not significantly differ, P > 0.6 for both paired t- and signed-rank tests.

Older females. Representative older female serum LH and FSH concentration time series are shown in Fig. 1, E and F. The individual older subject ApEn(FSH) – ApEn(LH) values are shown in Fig. 2 (right). Notably, as indicated in Table 1, for the postmenopausal group the FSH-LH irregularity difference vanished, with ApEn(FSH) – ApEn(LH) = 0.008 ± 0.205; ApEn(LH) was insignificantly different from ApEn(LH), P > 0.9 for both paired t- and signed-rank tests. In contrast, FSH levels were higher than mean LH levels, P < 0.005, for both signed-rank and paired t-tests.

Finally, we compared (t-test) combined younger vs. older females as another means to determine differences between these two groups. ApEn(FSH) – ApEn(LH) was higher in the younger females, P < 0.002; ApEn(LH) was greater in the older subjects compared with the younger cohort, P < 0.005; and there was no significant group difference based on ApEn(FSH) values, P > 0.65. For both FSH and LH, mean concentrations for the older subjects were higher than for the younger subjects, P < 0.001, consistent with the well-known rise in these levels postmenopaually.

Males. Representative LH and FSH serum concentration time series are shown in Fig. 1, G and H (younger male) and I and J (older male). Results of linear correlation analysis of age to ApEn(FSH) – ApEn(LH), as well as to ApEn and mean serum levels for each of FSH and LH, are shown in Table 2. Figure 3 displays ApEn(FSH) – ApEn(LH) individual subject values as a function of age, with the corresponding regression line. Both ApEn(FSH) – ApEn(LH) and ApEn(LH) showed
highly significant correlations with age. In contrast, the mean serum levels showed insignificant correlations. Furthermore, when all 11 males age <60 yr were combined into a single group, ApEn(FSH) \( - \) ApEn(LH) was positive for each subject, with ApEn(FSH) \( = \) 1.604 \( \pm \) 0.126 greater than ApEn(LH) \( = \) 1.118 \( \pm \) 0.232, \( P = 0.0012 \), paired t-test, \( P = 0.0005 \), signed-rank test. In contrast, for the six older males (>60 yr), ApEn(FSH) \( - \) ApEn(LH) \( = \) 0.010 \( \pm \) 0.134, with ApEn(FSH) \( = \) 1.701 \( \pm \) 0.062 insignificantly different from ApEn(LH) \( = \) 1.711 \( \pm \) 0.107, \( P > 0.85 \) for both the t-test and signed-rank test.

**DISCUSSION**

One primary finding is that individual serum FSH concentration time series are consistently and significantly more irregular than corresponding LH series on a per-subject basis in younger females and in males age <60 yr. Specifically, when results from both sexes were combined, 34 of 35 of these study subjects exhibited more irregular FSH than LH concentration dynamics. This result takes on added interest given the general 1:1 correspondence between primary LH and FSH pulses for both males and females. Thus the regularity

<table>
<thead>
<tr>
<th>ApEn and serum LH and FSH concentrations: females</th>
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<tbody>
<tr>
<td>EFol</td>
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<tr>
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<tr>
<td>ApEn(FSH) ( - ) ApEn(LH)</td>
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<tr>
<td>ApEn(LH)</td>
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<tr>
<td>ApEn(FSH)</td>
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<td>Mean serum level, IU/l</td>
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<td>LH</td>
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Values are means \( \pm \) SD. ApEn, approximate entropy; LH and FSH, luteinizing and follicle-stimulating hormones, respectively; EFol, early follicular; LFol, late follicular; MLut, midluteal; Y, younger; PostMen, postmenopausal. Serum level means are of 144 samples collected at 10-min intervals over 24 h.
The difference identified here is basically in a subordinate level of activity. The capability to quantify this difference in irregularity allows one explicit means to assess both typicality and atypicality (pathophysiology) of the FSH-LH joint dynamics and of changes in these dynamics, e.g., with aging. Such assessment can be made either at the secretory level or at the more clinically available serum concentration level, as studied herein, where clear serial features of hormone release are often far less evident. Hence, statistical appraisals similar to those undertaken above can be applied to a variety of investigations of the GnRH-LH-FSH network that are of potential scientific and clinical interest.

A second primary observation is that the difference in the extent of FSH and LH irregularity vanishes postmenopausally, i.e., that $\text{ApEn}(\text{FSH}) - \text{ApEn}(\text{LH})$ becomes insignificantly different from zero. We can thus evaluate the longitudinal evolution of $\text{ApEn}(\text{FSH}) - \text{ApEn}(\text{LH})$ on a per-subject basis, as one potential marker for menopause (commented on further below).

The third primary finding is that males exhibit results qualitatively similar to those of females, both in the consistency of irregularity differences between FSH and LH serum concentration dynamics in subjects of age <60 yr and in the diminution of this difference in older subjects. Therefore, the potential to detect (a)typical FSH-LH dynamics and changes in these dynamics, via FSH and LH irregularity comparisons, likely applies equally well to males. Indeed, there may be relatively broad utility of this statistical perspective in males, because mean serum FSH and LH levels do not significantly change with advancing age, thus requiring alternative statistical means of elucidating FSH-LH axis evolution. Furthermore, these data provide additional evidence for pronounced quantitative shifts in male reproductive secretory dynamics with aging, in conjunction with serum concentration irregularity and asynchrony shifts with aging previously seen for the LH-testosterone axis (19).

It is essential to note that, unlike an earlier analysis in sheep (11), in the present study we are not directly assessing dynamic secretory differences between FSH and LH. Given that LH and FSH were measured via different assays (with different variances) and have distinct clearance rates, we do not presently attempt to compare LH secretory irregularity to FSH secretory irregularity. The potential utility of the above results is that, in the human, for whom the noisier (postcon- volved) serum concentration series is all that is readily available, such data already are suitable for analysis in a quantitatively valid manner to define differences among cohorts.

Physiologically, although FSH secretion may in part reflect a constitutive, perhaps non-GnRH-dependent process (12), it has been generally accepted that FSH is also released in some measure in discrete episodic bursts, presumably reflecting a GnRH-dependent regulated secretory pathway. However, the identification and characterization of discrete FSH pulses have proved to be a formidable task, as seen in Fig. 1. The specific difficulties with the assessment of episodic FSH release have been reviewed in some detail (1, 2, 25) and relate in great part to the slow metabolic clearance of the hormone. This reinforces the need for techniques to statistically assess a degree of more subtle structure in FSH serial dynamics, e.g., via ApEn, apart from a requirement to do pulse identification first.

Within the younger female group, both Figs. 1 and 2 and Table 1 suggest the possibility that the irregularity of FSH and LH midluteal phase dynamics may differ from that during both the early follicular and late follicular phase. Furthermore, comparisons of the re-

Table 2. Linear correlations between age and ApEn and mean serum LH and FSH levels: males

<table>
<thead>
<tr>
<th></th>
<th>Pearson r</th>
<th>Significance, P</th>
<th>All-Subject Mean</th>
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<tbody>
<tr>
<td>$\text{ApEn}(\text{FSH}) - \text{ApEn}(\text{LH})$</td>
<td>-0.745</td>
<td>0.0006</td>
<td>0.311 ± 0.331</td>
</tr>
<tr>
<td>$\text{ApEn}(\text{LH})$</td>
<td>0.768</td>
<td>0.0004</td>
<td>1.327 ± 0.350</td>
</tr>
<tr>
<td>$\text{ApEn}(\text{FSH})$</td>
<td>0.192</td>
<td>0.46</td>
<td>1.639 ± 0.116</td>
</tr>
<tr>
<td>Mean serum level, IU/l</td>
<td></td>
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<tr>
<td>LH</td>
<td>0.112</td>
<td>0.67</td>
<td>3.41 ± 1.50</td>
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<tr>
<td>FSH</td>
<td>0.216</td>
<td>0.41</td>
<td>4.49 ± 2.55</td>
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Values are shown for 17 male subjects.
Prospective data sets of which A, C, and G of Fig. 1 are a representative example suggest that young males may be characterized by gonadotropin dynamics distinct from those in any of the young female phases. These possible differences, taken together with the consistency and parallelism of the present ApEn(FSH) — ApEn(LH) findings, underscore the need to ultimately determine both 1) physiological components of the LH-FSH subnetwork common to males and to females and 2) a single common physiological source, presuming that such exists, for the changes with aging in this subnetwork. An extensive delineation of young females into (phase stage) subgroups by irregularity awaits future studies, with larger subgroup sizes. Further studies should also clarify whether the rate of decrease of ApEn(FSH) — ApEn(LH) with increasing age in males is nearly constant until age 60, or whether, instead, subgroups of young (20–30 yr), middle-aged (30–60 yr), and older (>60 yr) males form more sharply distinct classes, as possibly suggested by Fig. 3.

Neuroendocrine considerations. Much of the basic physiological evidence suggesting that age does directly affect reproductive neuroendocrine function has come from studies in the rat (4, 9, 23, 34, 35). These investigations have identified alterations in both the anterior pituitary and the hypothalamus, for example, implicating GnRH in several explicit contexts, such as diminished pituitary responsiveness to exogenously administered GnRH in older rats in vivo (34) and in vitro (23), and irreversible defects in hypothalamic GnRH release mechanisms (35), with deficits in catecholamine turnover (34) and decreased GnRH neuronal c-fos expression (9). Nonetheless, the precise neuroendocrine mechanisms that drive or underlie such age-related changes remain largely unresolved. Indeed, there remains considerable controversy as to the genesis, or pacemaker, of menopause. A principal, long-held view is that the exhaustion of ovarian follicles triggers and precedes hypothalamic-pituitary changes (33). An alternative, more recently argued perspective is that altered temporal central nervous system signal organization precedes and triggers ovarian follicle exhaustion (see Ref. 37 for a comprehensive review). Although the present clinical study does not resolve this controversy, the results herein are consistent with a potentially relevant inference linking mechanism to statistical changes. On the basis of mathematical analysis of several models similar to the MIX(p) composite oscillator-noise process defined in Ref. 13, we can analytically establish that loss of synchrony or control at the neuronal firing level would often be first manifested qualitatively in an apparent muddying of pulse clarity at the macroscopic level of secretory episodes, i.e., first enhancing subordinate pulse features and nonmonotonic, somewhat “random” activity before subsequent apparent changes in primary pulse amplitudes and frequencies that only emerge with a substantially further loss of synchrony. Such presumptive degradation of pulse clarity would typically correspond to increasing irregularity (greater ApEn) for each individual hormone in question, both at the secretory level and at the serum concentration level, e.g., for LH as seen herein.

Although not known definitively, possible sources for such loss of synchrony could include the following. GnRH secretion is regulated by multiple neurotransmitters and neuropeptides (8). During middle age, yet still perimenopausally, the synchronized and interactive patterns of neuromodulation break down (36), manifested in such clinical features as hot flashes in women, and more directly in rodents, via changes in neurotransmitter receptor densities and levels of mRNAs that encode GnRH-regulating neuropeptides (37). As well, several neuropeptides that are abundantly expressed in the suprachiasmatic nuclei (SCN) of the hypothalamus, essential circadian pacemakers, send projections to GnRH neurons (6, 28); thus either the deterioration in the SCN or the coupling to its outputs could be linked with subsequent loss of synchronous timing (36) and resultant greater irregularity.

Furthermore, the present analysis affords a separate perspective on the long-held belief that the GnRH pulse generator slows markedly under the influence of luteal phase concentrations of serum progesterone, in that the mean luteal phase ApEn(LH) value is decidedly lower than that for the two follicular phases, as seen in Table 1, quantifying the apparent greater regularity of LH release during the luteal phase. From a mathematical modeling orientation, such a decrease in irregularity can correspond to either a decrease in event (pulse) frequency or suitable alterations in pulse character apart from frequency changes, e.g., changes in pulse shape or amplitude variation. The latter correspondence is consistent with several recent pathophysiological findings (3, 24).

Moreover, the follicular phase of young women with higher ApEn(LH) is most similar endocrinologically to the postmenopausal status, in that both estrogen and progesterone concentrations are low. This observation, combined with the moderate lowering of ApEn(LH) in the late-follicular phase and the more pronounced lowering of ApEn(LH) in the midluteal phase (when estrogen in the former case and estrogen combined with progesterone in the latter case are both elevated), suggests but does not prove that estrogen also controls ApEn(LH), at least in part. To more directly distinguish this from an age effect, a suitable study would involve giving postmenopausal women estrogen and/or progesterone and observing the ApEn response in treated individuals. However, a decline in estrogen with aging will not account for the male age-related effect, because men typically show a small gradual increase of estradiol concentrations in the course of healthy aging (29).

Potential applications. Characterization of irregularity of both LH and FSH singly, as well as jointly, could be employed to evaluate a variety of disorders and the efficacy of therapeutic intervention. Among syndromes in which mean LH and/or FSH levels are raised, study of polycystic ovary disease from this perspective could be useful, including a possible refinement of this disease into subclasses, in which irregularity of secretory patterns may delineate and correspond to clinically
observed separate presentations. Furthermore, monitoring changes in the irregularity difference between FSH and LH may be consequential in determining the time until onset of menopause, often an important determinant in hormonal therapy vs. surgical (hysterectomy) options in a patient with perimenopausal menorrhagia. The most vivid difference seen in the present results in ApEn(FSH) — ApEn(LH) was in comparisons of younger midluteal with the postmenopausal subjects. This then suggests a longitudinal study of the behavior of the difference ApEn(FSH) — ApEn(LH) during the midluteal cycle, in young women and as women become perimenopausal, as a potential marker of time until menopause. There are at least two important questions here. First, does ApEn(FSH) — ApEn(LH) typically decrease slowly and continuously to 0 over a multi-year window, or, instead, decrease more abruptly as menopause becomes imminent? Second, if one can establish that a decrease in Ap(FSH) — Ap(LH) precedes the perimenopausal rise in mean FSH and LH levels, then the present perspective would have considerable clinical implications, because widely applicable, firm quantitative predictors of menopausal onset appear to be lacking.

Among syndromes in which mean LH and FSH levels are lowered, unexplained anovulation could be analyzed to determine possible atypicality in the extent of irregularity of biorhonal secretion. A calculation of LH and FSH irregularity in serum could be employed to evaluate onset and recovery from anorexia nervosa, a potential marker of time until onset of menopause, often an important determinant in hormonal therapy vs. surgical (hysterectomy) options in a patient with perimenopausal menorrhagia. The most vivid difference seen in the present results in ApEn(FSH) — ApEn(LH) was in comparisons of younger midluteal with the postmenopausal subjects. This then suggests a longitudinal study of the behavior of the difference ApEn(FSH) — ApEn(LH) during the midluteal cycle, in young women and as women become perimenopausal, as a potential marker of time until menopause. There are at least two important questions here. First, does ApEn(FSH) — ApEn(LH) typically decrease slowly and continuously to 0 over a multi-year window, or, instead, decrease more abruptly as menopause becomes imminent? Second, if one can establish that a decrease in Ap(FSH) — Ap(LH) precedes the perimenopausal rise in mean FSH and LH levels, then the present perspective would have considerable clinical implications, because widely applicable, firm quantitative predictors of menopausal onset appear to be lacking.

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