0021-972X/88/6704-0832$02.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 67, No. 4
Printed in U.S.A.

Statistical Evaluation of Coincident Prolactin and Luteinizing Hormone Pulses During the Normal Menstrual Cycle*

DONALD K. CLIFTON, SEZER AKSEL, WILLIAM J. BREMNER, ROBERT A. STEINER, AND MICHAEL R. SOULES

Department of Obstetrics and Gynecology (D.K.C., W.J.B., R.A.S., M.R.S.), Physiology and Biophysics (R.A.S.), and Zoology (R.A.S.), University of Washington, Seattle, Washington 98195; and the Department of Obstetrics and Gynecology, University of South Alabama (S.A.), Mobile, Alabama 36688

ABSTRACT. The purpose of this work was 2-fold. First, we sought to develop statistical criteria by which it could be established that the coincident occurrence of pulses of two different hormones exceeds that which would occur by chance alone, thereby suggesting that secretion of the two hormones is either coupled or controlled from a single source generator. Using computer simulations of uncoupled pulse generators operating at different frequencies, we were able to derive the appropriate statistical criteria and to apply them to achieve our second objective, to determine whether the occasional coincidence of plasma LH and serum PRL pulses that occurs throughout the menstrual cycle in normal women exceeds that which would happen by chance. The results of the computer simulations indicated that pulses emanating from two completely independent oscillators will occur coincidently at a predictable rate, despite the fact that the generator sources are not coupled; moreover, the rate of coincidence is increased when the pulse frequency of one of the source generators is increased. Using this knowledge and the statistical criteria we derived, we analyzed the coincidence of LH and PRL pulses in five normal women during their early follicular, late follicular, and midluteal phases and in another five women during their late luteal phase. We found that the number of PRL pulses that occurred coincidently with LH pulses consistently exceeded that which would be predicted if the two pulse generators were operating completely independently of one another; however, only during the late follicular and late luteal phases was the coincidence level between LH and PRL pulses sufficiently high in a sufficient number of women to conclude that there was coupling between the pulse sources. These studies suggest, first, that stringent and rigorous statistical criteria must be applied to the analysis of spontaneously coincident secretory phenomena before it can be deduced that two pulse generators are indeed coupled, and second, that the pulse generators governing the secretion of PRL and LH are probably coupled, at least during certain phases of the menstrual cycle. (*J Clin Endocrinol Metab* **67:** 832, 1988)

THE SECRETION of most, if not all, adenohypophyseal hormones occurs in a pulsatile fashion under the influence of discharge of hypothalamic hormones; however, little is known about the factors that contribute to this mode of episodic secretion. Under certain conditions, pulsatile release of one pituitary hormone occurs simultaneously with that of another, as has been reported to be the case for LH and PRL in both humans and nonhuman primates (1–5). The detailed relationship between LH and PRL pulses during the normal menstrual cycle remains ill defined. Bäckström *et al.* (3) studied the plasma patterns of LH and PRL in normal women during 6-h segments. They reported that, overall, 70% of the PRL pulses were associated with an LH pulse. Whether this association varies with the phase of the cycle and whether a 70% coincidence significantly exceeds that which would occur by chance alone is uncertain, but these observations suggest that the gonadotrophs and lactotrophs either interact with each other or share some common mode of regulation. Indeed, the basic assumption that coincidence between LH and PRL secretion events implies coupling of their pulse generators has not been rigorously examined. Pulses emanating from two completely independent source generators will occur coincidently simply by chance at some predictable rate.

The purpose of this work was, first, to develop statistical criteria by which it could be established that the coincident occurrence of pulses of two different hormones exceeds that which would occur by chance alone, thereby establishing that the secretion of the two oscillators is either coupled or controlled from a single source generator. Second, we applied these criteria to determine whether the coincidence of LH and PRL pulses occurred more frequently than would be predicted by chance alone

Received February 2, 1988.
Address requests for reprints to: Donald K. Clifton, Department of Obstetrics and Gynecology, RH-20, University of Washington, Seattle, Washington 98195.
* This work was supported by NIH Grants R01-HD-18967-03 (to M.R.S.), P50-HD-12629-07 (to W.J.B.), R01-HD-12625-08 (to R.A.S.), Clinical Research Center grant RR-37, and the V.A.

and whether their coincidence changed during the normal menstrual cycle in women.

Materials and Methods

Subjects

Ten normal women, between the ages 24 and 34 yr, were studied. The study was approved by the Human Subjects Committee of the University of Washington, and informed consent was obtained from each women. These women were within ± 10% of ideal body weight (Metropolitan Life tables, 1980) and had regular menstrual cycles, normal basal body temperature charts, and normal serum PRL (<20 μg/L) and progesterone [>12 ng/mL (>38 nmol/L) in the midluteal phase] levels in a menstrual cycle preceding this study. The women were taking no medications and had not received any hormone therapy within the previous 12 months.

Protocol

Serum patterns of LH and PRL were determined during admissions (24 h each) to the University of Washington Clinical Research Center. Five women were admitted three times each during two cycles; the phases studied were early follicular (EF; days 1–4), late follicular (LF; days 9–12), and midluteal (ML; days 21–24). Another five women were admitted once in the late luteal (LL; days 25–28) phase of their cycle. During each admission, the women remained in bed, with caffeine and smoking prohibited. Blood samples (5 mL) were obtained through an indwelling iv catheter every 20 min for 24 h and then processed to provide serum for LH and PRL measurements.

Hormone assays

Serum samples were analyzed for LH using reagents obtained from the National Hormone and Pituitary Program, NIDDK; LER-907 was used as the reference preparation. The sensitivity of the assay was 6 μg/L, with intra and interassay coefficients of variation of 5.5% and 8.4%, respectively. The NIDDK human PRL kit (RP-1 standard and hPRL-3 anti-PRL serum) was used to determine serum PRL concentrations. The intraassay coefficient of variation was 6.5%, and the interassay variability was 14.8%. The sensitivity of the PRL assay was 1 μg/L. All samples from an individual woman were analyzed in duplicate in a single assay.

Pulse analysis

An adaptive threshold method (DC3) was used to determine the time of occurrence and amplitude of hormone pulses. A pulse was defined as an increase from a local minimum to a local maximum that was greater than a threshold value. The correct threshold was determined in an iterative manner. Initially, the threshold was set at 2.5 times the mean SD of the sample replicates, and the number of pulses in the data set was determined. Based on the estimated number of pulses, the threshold was readjusted according to the following formula: $T = S \times (5.518 + F \times [-0.3519 + F \times (0.01339 - 0.0002478 \times F)])$, where T is the threshold, S is the SD of the replicates, and F is 100 × (number of pulses detected last time)/(number of samples in the data set). The analysis then was repeated with the new threshold. If the number of pulses detected was different from the number found on the previous pass, the procedure was repeated. This iterative procedure was continued until the number of pulses detected stabilized. [The formula for threshold was determined empirically based on computer simulations (6).]

The performance of the DC3 pulse detector was evaluated by having it analyze computer-simulated LH pulses that were corrupted by simulated assay error (7). The clearance rate used for the simulations was equivalent to a LH half-life of 50 min; basal LH secretion (*i.e.* low level secretion of LH between pulses) was not included in our simulation model (8, 9). Pulse amplitude and interpulse interval varied randomly, with a uniform distribution, from 50–150% of the mean value. Seventy-two samples were obtained from each set of simulated LH patterns at a rate equivalent to a sampling interval of 20 min. Assay measurements were simulated by adding Gaussian-distributed random values to the sample values; this was done in duplicate for each sample, simulating duplicate assay measurements. The assay error for any particular sample had a SD equal to the coefficient of variation (CV) of the assay times sample value. For each simulated data set, the number of pulses detected was compared with the number generated. When fewer pulses were detected than generated, the difference between the number of pulses generated and the number of pulses detected was used as an indicator of false negatives. Conversely, when more pulses were detected than generated, the difference between pulses detected and generated was used as an indicator of false positives. It should be noted that these error estimates may be artificially low, since a true false positive in the same data set could cancel a true false negative, making it appear that no error occurred.

Table 1 illustrates the performance of the DC3 detector at 3 different simulated assay CVs and 5 different pulse frequencies. With an 8% CV, DC3 provided mean estimates of pulse frequency that were slightly low, but accurate within half of a pulse per data set. The highest false negative rate occurred when 4 pulses were present: 9 of 200 pulses were missed. The maximum number of pulses missed in any 1 of the 50 data sets generated at each pulse frequency was essentially independent of the pulse frequency, varying between 1–2 pulses. No false positives occurred at an 8% CV among the 18,000 sample points that were generated. Performance of DC3 at a CV of 16% was similar to its performance at 8%, except for the presence of some false positives (3 in 18,000 samples) and more false negatives at the higher frequencies (≤16 pulses/data set). The trend toward more false negatives at higher frequencies and increased false positives continued at an assay CV of 24%; however, even with this large assay variance, DC3 provided mean estimates that were accurate within 1 pulse in simulations containing up to 16 pulses.

Statistical evaluation of coincidence

One major issue that we sought to resolve was whether there is a significant degree of synchrony between LH and PRL

TABLE 1. Performance of the DC3 pulse detector

% Intraassay CV (stimulated)	Pulses generated	Pulses detected[a]	False negatives[b]		False positives[c]	
			Rate (%)[d]	Maximum	Rate (%)[e]	Maximum
8	4	3.8 ± 0.4	4.5	2	0.0	0
	8	7.8 ± 0.4	2.0	1	0.0	0
	12	11.8 ± 0.4	1.3	2	0.0	0
	16	15.7 ± 0.4	1.6	1	0.0	0
	20	19.6 ± 0.5	1.8	2	0.0	0
16	4	3.8 ± 0.4	3.5	1	0.0	0
	8	7.8 ± 0.4	1.8	1	0.0	0
	12	11.8 ± 0.4	1.7	1	0.0	0
	16	15.6 ± 0.6	3.4	3	0.027	1
	20	19.4 ± 1.1	2.5	2	0.055	1
24	4	4.0 ± 0.3	1.0	1	0.055	1
	8	7.9 ± 0.5	2.0	2	0.083	1
	12	11.6 ± 0.6	3.2	2	0.027	1
	16	15.2 ± 1.5	6.3	6	0.22	1
	20	18.3 ± 2.3	9.5	8	0.33	4

Shown are results of 50 computer simulations for each combination of intraassay CV and pulses generated. LH pulses with a 50-min half-life were sampled at 20-min intervals for a 24-h period (72 samples/data set) and assayed in duplicate. Pulse amplitude and interpulse interval varied randomly from −50% to +150% of the mean value.

[a] Each value represents the mean ± SD obtained from 50 simulated data sets.

[b] False negatives were defined as the difference between the number of pulses generated and the number of pulses detected when fewer pulses were detected than generated.

[c] False positives were defined as the difference between the number of pulses detected and the number of pulses generated when more pulses were detected than generated.

[d] The total number of false negatives that occurred in 50 simulated data sets divided by the total number of pulses generated in those data sets.

[e] The total number of false positives that occurred in 50 simulated data sets divided by the total number of samples in those data sets (50 × 72 = 3600).

pulses at various times during the menstrual cycle. Even when two pulse systems operate independently of one another, the pulses they generate will sometimes be coincident simply by chance. Therefore, the occurrence of coincident pulses may or may not be indicative of coupling between pulse sources. (We considered LH and PRL peaks to be coincident if their peaks, as determined by our pulse detection method, occurred within one sample interval of each other.) We tested the null hypothesis that LH and PRL pulses are generated independently against the alternative hypothesis that there is some degree of coupling between the two.

We used Monte Carlo computer simulations to estimate the probabilities associated with coincident PRL and LH pulses when there is no coupling between the two generators. The simulation program generated two independent sets of data, each containing a pseudorandom number of pulses distributed across 73 sample points. Pulses were assigned to the sample points on a pseudorandom basis, with the constraint that they be separated from each other by at least 1 sample point to which a pulse was not assigned. After both simulated data sets were generated, they were compared to determine the number of coincident pulses. This information along with the number of pulses that each of the 2 data sets contained were stored into a 3-dimensional array ([number of pulses in first data set (np1)] × [number of pulses in second data set (np2)] × [number of coincident pulses (nc)]) of frequencies. This process was repeated 150,000 times. When the program was terminated, a second program read the frequency information and calculated, for each combination of np1 and np2, the probability that at least nc coincident pulses would occur. From these probabilities a table was constructed to determine, at $\alpha = 0.05$, the number of coincident pulses that must occur within an individual to reject the hypothesis that PRL and LH pulses occurred independently (*i.e.* not coupled). A binomial probability calculation then was used to determine if a significant number of women had a significant degree of coincidence between LH and PRL pulses within each cycle phase.

The second major issue to be resolved was whether the degree of synchrony between pulses of LH and PRL varied as a function of the phase of the menstrual cycle. A measure of excess coincidence was used to determine this. The percentage of PRL pulses that were coincident with LH pulses was computed for each woman at each phase of the cycle and then was subtracted from the percentage of coincident LH and PRL pulses that we would have expected had the two pulse sources not been coupled. The expected percent coincidence is a function of the individual's LH pulse frequency and was calculated based on the results of the computer simulations described above. A Friedman two-way analysis of variance (subject *vs.* phase of cycle) then was used to test for significant changes in excess coincidence across cycle phases.

Results

The results of the Monte Carlo simulations are summarized in Table 2. This table shows the number of

TABLE 2. Critical number of coincident pulses based on Monte Carlo simulations

No. of PRL pulses	No. of LH pulses																
	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
3			3[a]	3	3	3	3	>[b]	>	>	>	>	>	>	>	>	>
4		3	3	3	4	4	4	4	4	>	>	>	>	>	>	>	>
5	3	3	3	4	4	4	4	5	5	5	5	>	>	>	>	>	>
6	3	3	4	4	4	5	5	5	5	5	6	6	6	6	>	>	>
7	3	3	4	4	4	5	5	5	6	6	6	7	7	7	>	>	>
8	3	4	4	5	5	6	6	6	7	7	7	8	8	8	8	>	>
9	3	4	4	5	5	6	6	7	7	7	7	8	9	9	9	9	>
10	>	4	5	5	6	6	7	7	7	7	8	9	9	9	9	10	10
11	>	4	5	5	6	6	7	7	8	8	9	9	10	10	10	11	11
12	>	4	5	5	6	7	7	7	8	9	9	10	10	10	11	12	12
13	>	>	5	6	7	7	7	8	9	9	10	10	11	11	12	12	12
14	>	>	>	6	7	7	8	9	9	10	10	11	11	12	12	13	13
15	>	>	>	6	7	8	8	9	10	10	11	11	12	12	13	13	14
16	>	>	>	6	7	8	9	9	10	10	11	12	12	13	13	14	15
17	>	>	>	>	>	8	9	9	10	11	12	12	13	13	14	14	15
18	>	>	>	>	>	>	9	10	11	12	12	13	13	14	14	15	16
19	>	>	>	>	>	>	>	10	11	12	12	13	14	15	15	16	16

This table was constructed from 150,000 stimulations, each containing a pair of data sets consisting of 73 sample points each (see *Materials and Methods* for details).

[a] The values indicate the minimum number of coincident pulses needed to reject the hypothesis that the pulse generators are independent (uncoupled) at $\alpha = 0.05$.

[b] The probability is greater than 0.05 that all the pulses will be coincident, even when the pulse generators are independent.

pulses that must be coincident before one can be confident (at the $\alpha = 0.05$ level) that the two pulse generators are not independent. Note that when one of the pulse frequencies is high and the other is low, a high percentage of the pulses must be coincident before statistical significance is reached. In fact, in extreme instances, even when all of the lower frequency pulses are coincident with the higher frequency ones, it is not possible to conclude on a statistical basis (at $\alpha = 0.05$) that the two generators are coupled (*i.e.* not independent).

Figure 1 illustrates serum LH and PRL pulse patterns in women at the various stages of the menstrual cycle; data from all of the women are summarized in Table 3. The frequency of both LH and PRL pulses underwent significant ($P < 0.05$) changes during the menstrual cycle, as determined by a two-way (subjects *vs.* cycle stages) analysis of variance. Pulse frequency was highest during the LF phase and lowest during the luteal phase for both hormones. In addition, mean LH levels were significantly higher during the follicular phase than during the luteal phase ($P < 0.01$). LH pulse amplitude, PRL pulse amplitude, and mean PRL levels did not change significantly during the menstrual cycle. (The LL data set was excluded from the above analyses since it was obtained from different women than the EF, LF, and ML phase data sets.)

In both the LF and LL phases there was a sufficient number of coincident pulses in three of five women to conclude, based on the results shown in Table 2, that their PRL and LH pulse generators were not acting independently (see Table 4). Three of five women with coincident LH and PRL pulses is a greater incidence than one would expect to occur by chance ($P < 0.05$) if there were, in fact, no tendency among women at these stages of the cycle toward coupling of their PRL and LH pulse generators. Only one of five women in the EF phase and none of the women in the ML phase had a significant number of PRL pulses coincident with LH pulses.

Figure 2 shows the percent coincidence as a function of LH pulse frequency for the data in Table 4. Note that in 17 of 20 data sets, the percent coincidence was higher than would have been expected if the LH and PRL pulse generators were completely independent. While coincidence between PRL and LH pulses underwent dramatic variations during the menstrual cycle (Table 3), much of the change in coincidence could be attributed to the variations in LH pulse frequency. To demonstrate this, the effect of LH pulse frequency was removed from each individual coincidence estimate by subtracting the expected coincidence (*i.e.* the coincidence we would expect if the pulse generators were uncoupled) from the observed coincidence to provide an estimate of excess coincidence. As shown in Fig. 3, excess coincidence was constant during the EF, LF, and ML phases of the menstrual cycle. (Again, the LL data set was excluded since it was obtained from different women than the EF, LF, and ML phase data sets.)

Discussion

We used a statistical method to evaluate coincidence between the secretory pulses of two different hormones.

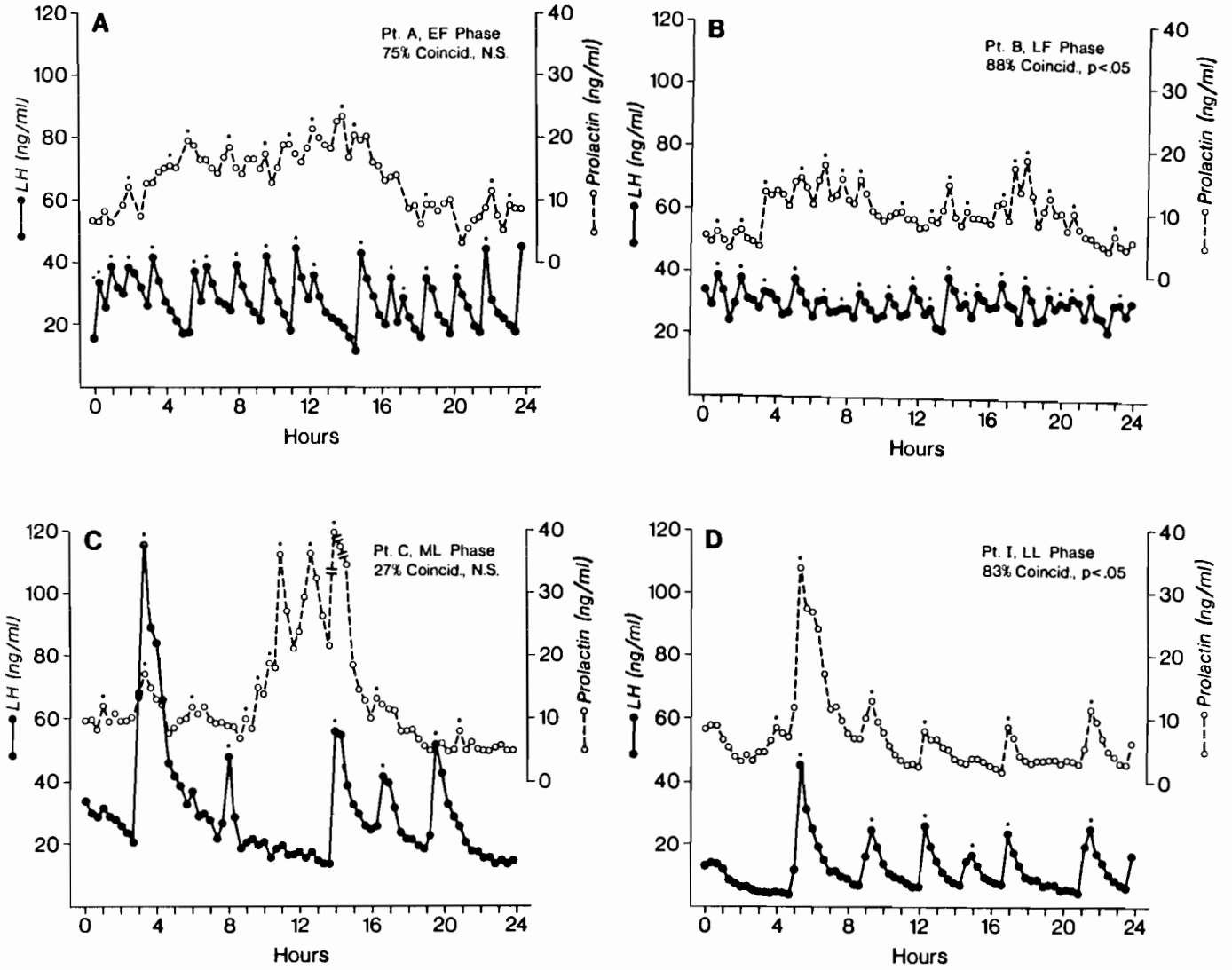

FIG. 1. Plasma LH and serum PRL pulse patterns in four women at different stages of the menstrual cycle. The *asterisks* indicate points identified as pulse peaks. (SI unit conversion: 1 ng/mL = 1 μg/L.)

TABLE 3. LH and PRL pulse characteristics in normal women at various times during the menstrual cycle

Cycle phase	Mean level (μg/L)		Pulse frequency (pulses/24 h)		Pulse amplitude (μg/L)	
	LH	PRL	LH	PRL	LH	PRL
EF	35.1 ± 8.8	9.0 ± 0.6	14.6 ± 1.5	11.0 ± 1.0	16.4 ± 1.9	4.0 ± 0.9
LF	36.6 ± 6.8	9.7 ± 0.6	17.6 ± 0.9	13.8 ± 1.6	12.5 ± 1.8	4.4 ± 0.4
ML	15.0 ± 4.2	10.4 ± 1.2	5.6 ± 0.6	9.4 ± 0.7	21.1 ± 6.1	6.1 ± 1.0
LL[a]	11.2 ± 1.5	9.6 ± 1.4	8.6 ± 1.2	8.6 ± 1.5	14.0 ± 3.6	11.1 ± 3.2

[a] LL data were collected from a group of women different from the group used for EF, LF, and ML data.

We found that a high coincidence value does not necessarily indicate coupling between hormone pulse generators. When the frequency of one pulse generator is high, it is highly probable that any given pulse from another, uncoupled generator will be coincident despite their independence. This is illustrated by the *straight line* in Fig. 2, showing that as LH pulse frequency increases, the expected percent coincidence between hormone pulses also increases, even when both generators are operating completely independently. It is important, therefore, to take into account the pulse frequency of both hormones as well as the percent coincidence when attempting to determine whether two pulse generators are coupled. Either the Monte Carlo procedure described here or

TABLE 4. Coincidence of serum PRL and LH pulses in normal women at various phases of the menstrual cycle

Subject	Cycle phase	No. of LH pulses	No. of PRL pulses	No. of coincident pulses	% PRL pulses coincident
A	EF	16	12	9	75
B		11	11	8[a]	73
C		18	12	8	67
D		17	7	6	86
E		11	13	8	62
Mean		14.6	11.0	7.8	72.6
SE		1.5	1.0	0.5	4.1
A	LF	18	11	9	82
B		20	17	15[a]	88
C		16	13	10	77
D		19	10	10[a]	100
E		15	18	14[a]	78
Mean		17.6	13.8	11.6	85.0
SE		0.9	1.6	2.7	4.2
A	ML	7	9	3	33
B		7	10	3	50
C		5	11	3	27
D		4	7	3	43
E		5	10	2	20
Mean		5.6	9.4	2.8	34.6
SE		0.6	0.7	0.2	5.4
F	LL	8	8	3	38
G		9	11	3	27
H		13	13	11[a]	85
I		6	6	5[a]	83
J		7	5	5[a]	100
Mean		8.6	8.6	5.4	60.6
SE		1.2	1.5	1.5	13.7

[a] Indicates occurrence of a significant number of coincident pulses.

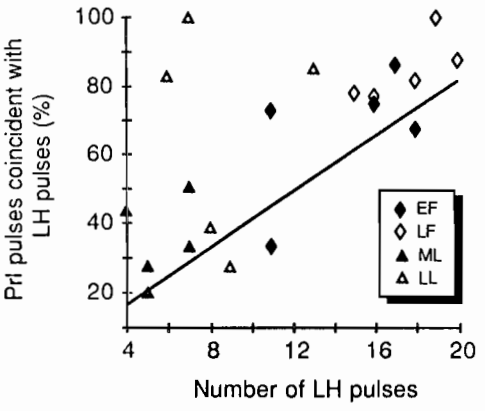

FIG. 2. The relationship between LH pulse frequency and the percentage of PRL pulses coincident with LH pulses during the EF, LF, ML, and LL phases of the menstrual cycle. Each *data point* represents the results obtained in one woman during a 24-h blood-sampling period. The *straight line* indicates the expected relationship (based on Monte Carlo simulations) between LH pulse frequency and percent coincidence between LH and PRL pulses if there was, in fact, no coupling between the LH and PRL pulse generators.

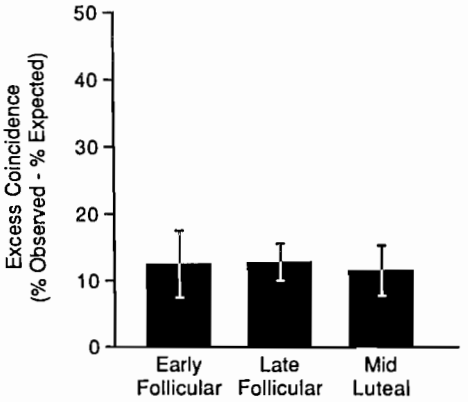

FIG. 3. Excess coincidence during the menstrual cycle. Excess coincidence is defined as the observed coincidence minus the expected coincidence based on Monte Carlo simulations. The *bars* represent the mean (±SE) results from five women in each cycle phase.

Table 2 (if 73 sample points are being evaluated) should be helpful to other investigators who are interested in assessing the significance of coincident hormone pulses.

The experimental results presented confirm the reports of others that a large percentage of PRL pulses appear to occur coincident with LH pulses in women. The observation by Bäckström *et al.* (3) that roughly 70% of the PRL pulses occur within 15 min of a LH pulse in normal women agrees well with our finding of an average 62% coincidence during the menstrual cycle. Braund and co-workers (5) also reported a high degree of synchrony between PRL and LH pulses (91%); however, their study was conducted during the midluteal phase, a time during which we found a relatively low degree of coincidence (35%). This discrepancy is probably due to their use of a less stringent criterion for defining a hormone pulse. They reported the occurrence of 2.7 LH pulses/6 h, which is almost twice as frequent as we report here. As mentioned above, the presence of more frequent LH pulses necessarily results in greater coincidence.

Although others have assumed that a high level of coincidence indicates that there is some coupling between LH and PRL, the evidence is less compelling when the data are examined by statistical criteria. In fact, during the EF phase, a time when the mean coincidence between PRL and LH was 72.6%, only one of five women had a hormone secretory pattern that could be identified as significantly different from that generated by completely independent pulse generators ($P < 0.05$). Only during the LF and LL phases did a significant number of women demonstrate a significant degree of coupling between LH and PRL pulses. This should not be taken as an indication that there is no coupling during other cycle phases, rather only that we were unable to confirm, by strict statistical criteria, coupling at these other times.

As was reported previously by us and others, LH and

PRL pulse frequencies change significantly during the menstrual cycle (3, 10–13). We also found significant changes in the percent coincidence between PRL and LH during the cycle. However, the dramatic variations in coincidence between LH and PRL pulses may be misleading, since most, if not all, of the change (from 85% in LF to 35% in ML) can be attributed to the alterations in LH pulse frequency.

When applying the type of analysis we describe here, one must keep in mind two important considerations. First, when the frequency of one pulse generator is high and that of the other is low, here are instances when even 100% coincidence would not be statistically significant. This is illustrated by subject D, in whom 86% of the PRL pulses were coincident with LH pulses. According to Table 2, even if 100% of subject D's seven PRL pulses had been coincident with her LH pulses, we would still not be able to conclude (at $\alpha = 0.05$) that there was a significant degree of coupling between PRL and LH. Second, when the pulse generators have a high degree of autocorrelation and are operating at approximately the same frequency, it is possible, on occasion, to observe a significant degree of coincidence in the absence of coupling between the generators (14). The implication of these two facts is that other criteria beyond simply identifying periods of coincident pulses must be used to firmly establish coupling. For example, demonstrating that either slowing or accelerating the pulse frequency of one oscillation affects the other similarly would provide a more persuasive argument.

In summary, the simulation results presented here suggest that caution must be exercised when drawing conclusions from pulse coincidence data. It is essential that proper statistical criteria be applied, because a high coincidence of pulsatile events can be misleading since this could occur by chance alone. Using Monte Carlo simulations, we were able to demonstrate that the LH and PRL pulse generators are probably coupled during the LF and LL phases. Table 2 and the procedures we have presented should prove useful in evaluating coupling between other hormone pulse generators.

Acknowledgments

The authors gratefully acknowledge the laboratory assistance of Ms. Florida Flor, Ms. Dorothy McGuiness, Ms. Dianne Schoenberg, and Ms. Nancy Cohen.

References

1. Belchetz P, Duffy B, Knobil E 1978 Identification of inhibitory and stimulatory control of prolactin secretion in the rhesus monkey. Neuroendocrinology 27:32
2. Wehrenburg WB, Ferin M 1982 Regulation of pulsatile prolactin secretion in primates. Biol Reprod 27:99
3. Bäckström CT, McNeilly AS, Leask RM, Baird DT 1982 Pulsatile secretion of LH, FSH, prolactin, oestradiol and progesterone during the human menstrual cycle. Clin Endocrinol (Oxf) 17:29
4. Cetel NS, Yen SSC 1982 Concomitant pulsatile release of prolactin and luteinizing hormone in hypogonadal women. J Clin Endocrinol Metab 56:1313
5. Braund W, Roeger DC, Judd SJ 1984 Synchronous secretion of luteinizing hormone and prolactin in the human luteal phase: neuroendocrine mechanisms. J Clin Endocrinol Metab 58:293
6. Clifton DK 1987 Objective evaluation of pulse detection methods by computer simulation. In Crowley Jr WF, Hofler J (eds) Episodic Hormone Secretion. Wiley and Sons, New York, pp 35–46
7. Clifton DK, Steiner RA 1983 Cycle detection: a technique for estimating the frequency and amplitude of episodic fluctuations in blood hormone and substrate concentrations. Endocrinology 112:1057
8. McIntosh RP, McIntosh JEA 1985 Amplitude of episodic release of LH as a measure of pituitary function analysed from the time-course of hormone levels in the blood: comparison of four menstrual cycles in an individual. J Endocrinol 102:231
9. Veldhuis JD, Guardabasso V, Rogol AD, Evans WS, Oerter K, Johnson ML, Rodbard D 1987 Appraising the nature of luteinizing hormone secretory events in man. Am J Physiol 252:E599
10. Midgley Jr AR, Jaffe RB 1971 Regulation of human gonadotropins. X. Episodic fluctuation of LH during the menstrual cycle. J Clin Endocrinol Metab 33:962
11. Yen SSC, Tsai CC, Naftolin F, Vandenberg G, Ajabor L 1972 Pulsatile patterns of gonadotropin release in subjects with and without ovarian function. J Clin Endocrinol Metab 34:671
12. Soules MR, Steiner RA, Clifton DK, Cohen NL, Aksel S, Bremner WJ 1984 Progesterone modulation of pulsatile luteinizing hormone secretion in normal women. J Clin Endocrinol Metab 58:378
13. Filicori M, Butler JP, Crowley Jr WF 1984 Neuroendocrine regulation of the corpus luteum in the human. Evidence for pulsatile progesterone secretion. J Clin Invest 73:1638
14. Cook TD, Campbell DT 1979 Quasi-Experimentation: Design and Analysis Issues for Field Settings. Rand McNally, Chicago, pp 295–339