Characterization of the Inappropriate Gonadotropin Secretion in Polycystic Ovary Syndrome

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Abstract To evaluate gonadotropin release in polycystic ovary syndrome (PCO), one or more of the following hypothalamic-pituitary function tests were performed on 24 patients with the syndrome. These tests included (*a*) the pulsatile pattern and day-to-day fluctuation of gonadotropin release; (*b*) effects of exogenous estrogen and antiestrogen (clomiphene) administration on gonadotropin release; and (*c*) pituitary responsiveness to maximal (150 μg) and submaximal (10 μg) luteinizing hormone-releasing factor (LRF) injections. In 10 of the 14 patients sampled frequently (15 min) for 6 h, luteinizing hormone (LH) levels were elevated above the concentration seen in normal cycling women (except the LH surge). These high LH concentrations appeared to be maintained by and temporally related to the presence of exaggerated pulsatile LH release, either in the form of enhanced amplitude or increased frequency. In all subjects, levels of follicle-stimulating hormone (FSH) were low or low normal, and a pulsatile pattern was not discernible. In four patients, daily sampling revealed marked day-to-day fluctuation of LH but not FSH. That the elevated LH levels were not related to a defect in the negative-feedback effect of estrogen was suggested by the appropriate fall of LH in four patients given an acute intravenous infusion of 17β-estradiol. This infusion had no effect on FSH levels. In addition, clomiphene elicited rises of both LH and FSH that were comparable to the ones observed in normal women given the same treatment. The clomiphene study also suggested that the positive-feedback mechanism of estrogen on LH release was intact when the preovulatory rises of 17β-estradiol induced appropriate LH surges. The elevated LH levels appeared to be related to a heightened pituitary responsiveness to the LRF. This was found in the 11 and 2 patients given maximal (150 μg) and submaximal (10 μg) doses of LRF, respectively. The augmented pituitary sensitivity for LH release correlated with the basal levels of both estrone ($P < 0.025$) and 17β-estradiol ($P < 0.02$). The net increase in FSH was significantly greater ($P < 0.001$) in the PCO patients than the normal women with maximal doses of LRF. With the smaller dose study, none of the injections had a discernible effect on FSH concentrations in either subject. The disparity between LH and FSH secretion could be explained by the preferential inhibitory action of estrogen on FSH release, coupled with a relative insensitivity of FSH release.

These data indicate that in these PCO patients the abnormalities of the hypothalamic-pituitary regulation of gonadotropin secretion was not an inherent defect but represented a functional derangement consequent to inappropriate estrogen feedback, which led to a vicious cycle of chronic anovulation and inappropriate gonadotropin secretion.

INTRODUCTION

The pathophysiology of polycystic ovary syndrome (PCO)[1] is poorly understood (1–9). An erratic or inappropriately elevated luteinizing hormone (LH) secretion with a relatively constant and low follicle-stimulating hormone (FSH) release has been found (10–13). It is not known whether this pattern of gonadotropin secretion is due to a primary defect in the hypothalamus-pituitary system or is a result of inappropriate feed-

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Received for publication 5 May 1975 and in revised form 20 November 1975.

[1] *Abbreviations used in this paper:* E_1, estrone; E_2, 17β-estradiol; FSH, follicle-stimulating hormone; LH, luteinizing hormone; LRF, luteinizing hormone-releasing factor; PCO, polycystic ovary syndrome.

back occasioned by the abnormal steroidogenesis of the polycystic ovary (14–19).

The recent demonstrations of the pulsatile nature of gonadotropin secretion (20–23) and its modulation by gonadal steroids (21, 23), together with the clinical application of hypothalamic hormones (24), have afforded new approaches in the delineation of hypothalamic-pituitary dysfunction. In addition, assessments of responses to the feedback action of estrogen and antiestrogen should be helpful in disclosing the components of aberration in the hypothalamic-pituitary-ovarian system in patients with PCO. The present report concerns the results of these investigations.

METHODS

One or more of the following studies were performed in a clinical research unit at University Hospital, University of California at San Diego, on 24 patients with PCO. In each the diagnosis was established by laparoscopy and ovarian biopsy. Table I summarizes the clinical data and studies that were performed on each patient. The women had received no medication for at least 3 mo before these investigations.

Analyses of gonadotropin pulses and long-term fluctuations. To determine the frequency and amplitude of gonadotropin fluctuation in this syndrome, serum LH and FSH levels were studied in 14 patients on samples drawn at 15-min intervals for 6 h through an indwelling venous catheter. A pulse was defined as an incremental change of gonadotropin levels of 20% or greater from nadir to peak of a pulse (22). In four patients the pattern of long-term gonadotropin fluctuations was assessed by analyses of daily gonadotropin levels measured for 14–34 days. In one of these subjects, daily 17β-estradiol (E_2), estrone (E_1), and progesterone levels were also quantitated.

E_2 feedback study. The acute negative-feedback effect of E_2 on the pulsatile gonadotropin rhythm was studied in four patients via a constant infusion of E_2 at a rate of 50 μg/h for 4 h, as described previously (23, 25). 6-ml blood samples were obtained at 15-min intervals for 16 h beginning 1 h before the start of the E_2 infusion.

Pituitary hormone release in response to stimuli. The quantitative and qualitative aspects of gonadotropin release in response to luteinizing hormone-releasing factor (LRF) (150 μg bolus) were assessed in 11 patients as described previously (26). Serum LH and FSH levels were measured on blood samples obtained at 15-min intervals for 2 h before and 3 h after the LRF administration. In addition, serum E_1 and E_2 concentrations were determined on samples drawn just before the LRF injection. For comparison, a similar study was performed on 11 normal women during both the early and later follicular phases of their menstrual cycles.

In two patients, the effect was evaluated of five repeated bolus injections at 2-h intervals of submaximal doses of LRF (10 μg) (27). Blood samples were obtained for LH and FSH determinations at 15-min intervals beginning 1 h before the first injection and continuing until 3 h after the fifth injection.

TABLE I

Summary of Studies Performed and Clinical Data on 24 Patients with PCO

Patient	Study					Age	P-A*	Wt.	Ht.	Menses‡	Hirsutism§	Ovary size‖
	Freq.	Daily	Estradiol infusion	LRF	Clomiphene							
						yr		*lb*				
1. S. A.	✓	✓				29	0-0	142	66	O	3+	Enlarged
2. E. A.	✓			✓		33	0-0	150	64	O	3+	Normal
3. K. B.	✓				✓	22	0-0	113	62	A	0	Enlarged
4. R. H.	✓		✓			28	0-0	209	63	O	4+	Enlarged
5. J. K.	✓					25	0-0	194	65	O	3+	Enlarged
6. J. L.	✓			✓		23	0-0	130	66	A	0	Enlarged
7. M. M.	✓				✓	25	0-0	135	63	O	0	Normal
8. T. N.	✓	✓	✓			26	0-0	124	67	O	0	Enlarged
9. C. P.	✓	✓	✓			25	0-0	140	68	O	2+	Normal
10. G. R.	✓					25	0-0	185	63	A	4+	Enlarged
11. L. V. S.	✓			✓		25	0-0	115	63	O	2+	Normal
12. J. M. S.	✓					26	0-0	114	59	O	0	Enlarged
13. J. B. S.	✓	✓	✓			31	0-0	110	61	O	0	Enlarged
14. V. W.	✓					22	0-1	136	68	O	0	Enlarged
15. D. B.				✓		23	0-0	95	60	A	2+	Enlarged
16. P. C.				✓		20	0-0	105	64	A	0	Normal
17. P. J.				✓		24	0-0	138	64	A	0	Enlarged
18. P. M.				✓		24	0-0	127	60	O	3+	Enlarged
19. S. M.				✓		26	3-0	196	65	A	1+	Normal
20. S. R.				✓		26	0-0	113	63	O	2+	Enlarged
21. L. C. S.				✓		28	0-0	170	66	O	0	Normal
22. C. Y.				✓		20	0-0	120	65	A	4+	Enlarged
23. R. G.					✓	22	0-0	120	62	A	0	Enlarged
24. L. K.					✓	31	0-0	122	65	O	0	Normal

* P—Parity, A—Abortion.

‡ O, oligomenorrhea; A, amenorrhea.

§ Facial hirsutism was graded on the number of regions involved (sideburns, upper lip, beard) according to Bardin and Lipsett (17).

‖ Via laparoscopy.

The effects of the antiestrogen clomiphene (100 mg/day for 5 days) were studied on gonadotropin secretion, and the temporal change in ovarian function were evaluated in four patients. For comparison, the same clomiphene treatment was given beginning in the early follicular phase (days 2–4) to four normally cycling women. Daily blood samples were obtained starting on the first day of clomiphene treatment and ending on the first day of vaginal bleeding. Serum concentrations of LH, FSH, E_2, and progesterone were analyzed.

Serum LH, FSH, E_2, E_1, and progesterone levels were measured by previously described radioimmunoassay procedures (23, 28–30). The relative potency of Second International Reference Preparation human menopausal gonadotropin to LER 907 was 38 mIU/μg for FSH and 210 mIU/μg for LH. For each patient all samples for a given study were run in the same assay.

For the 150 μg LRF studies, the areas circumscribed by the serum LH and FSH curves (above the base-line value) during the 3 h following the LRF injection were measured. This increment in response to LRF was used as an index for describing relative quantitative changes in hormone secretion. The area units were calculated by a computer program (31) and expressed as international units/milliliter per hour and milli-international units/milliliter per hour for LH and FSH, respectively.

The two-tailed Student's t test was used for statistical analyses.

RESULTS

Table II shows the mean levels of LH and FSH found in the PCO patients sampled frequently for 6 h. In 10 women the mean LH concentrations were in excess of 25 mIU/ml, while in four the mean levels were within the normal range found in women during the menstrual cycle (except LH surge [12]). No relationship was noted between the size of the patient's ovaries and the mean concentration of LH (Tables I and II). In all patients the mean FSH levels were in the low normal range for cycling women (12). During these 6-h studies, a marked degree of variability was found in the pulsatile fluctuation of LH but not FSH (Table II). Representative patterns are depicted in Fig. 1. The frequency of LH pulses varied from one to five, and the amplitude ranged from 5.5 to 31.1 mIU/ml during these studies. Within a given subject the pulse amplitude was relatively constant with the amplitude varying by more than twofold in only one subject (S. A.). In general, the pulsatile fluctuations of LH were exaggerated either in the form of an increase in frequency or amplitude in the patients with elevated basal LH concentrations. In the four patients with normal LH levels, the pulsatile LH patterns were similar to those found in normal women during the early follicular phase of the cycle (21). FSH levels remained relatively constant in all patients.

Table III shows the mean and coefficient of variation of serum LH and FSH concentrations found in the four patients sampled daily. In three of four women the mean daily LH concentrations were greater than 25 mIU/ml, and in the fourth subject (E. A.) it was 24.1 mIU/ml.

TABLE II

Serum LH and FSH Levels and Variation of Frequency and Amplitude of LH Pulses Measured during a 6-h Sampling Period at 15-min Intervals in 14 Patients with PCO

Patients	Serum LH					Serum FSH	
	Mean	Coefficient of variation	No. of pulses per 6 h	Pulse Min.	Pulse Max.	Mean	Coefficient of variation
	mIU/ml	%		*mIU/ml*		*mIU/ml*	%
1. S. A.	45.6	21.3	4	15.7	31.3	5.0	12.6
2. E. A.	20.4	11.7	1	—	5.7	9.3	8.2
3. K. B.	41.3	19.2	5	8.8	15.1	10.1	15.3
4. R. H.	45.7	9.0	2	9.8	13.7	13.2	0.73
5. J. K.	11.2	21.5	1	—	10.9	7.6	6.6
6. J. L.	26.6	30.0	3	8.5	15.0	6.5	16.6
7. M. M.	108.3	10.0	4	24.5	31.1	15.3	7.1
8. T. N.	53.5	8.7	2	10.3	11.8	11.1	8.2
9. C. P.	34.0	14.3	4	8.2	12.8	4.0	16.6
10. G. R.*	18.2	15.1	3	5.5	7.2	10.1	7.5
11. J. B. S.	26.0	8.8	3	12.7	14.5	12.2	33.4
12. L. V. S.	19.0	20.3	4	5.6	14.1	9.1	8.6
13. J. M. S.	30.1	18.1	2	6.4	7.8	7.2	0.80
14. V. W.	34.7	12.5	5	6.7	8.3	11.4	7.0
Mean	36.8	15.7	3.1	10.2	14.2	9.4	10.7
±SE	6.4	1.7	0.35	1.6	2.1	0.85	2.2

* 4-hour sampling.

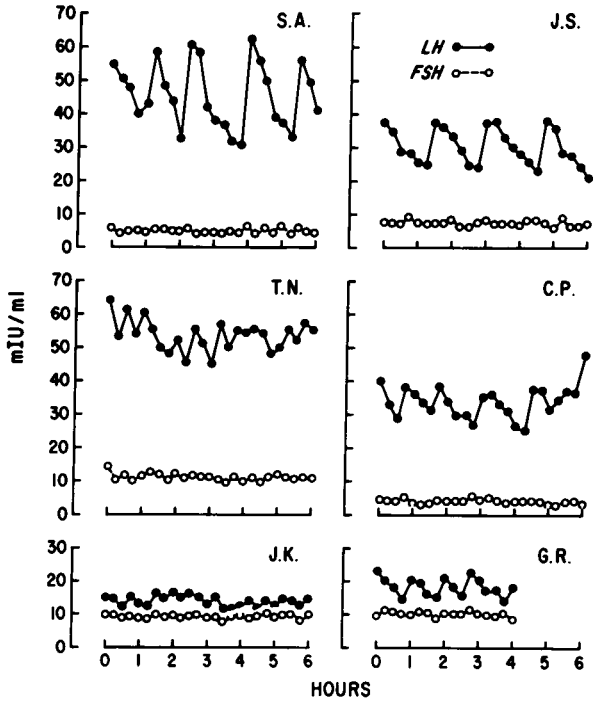

FIGURE 1 The representative patterns of pulsatile LH release (but not FSH) in six patients with PCO.

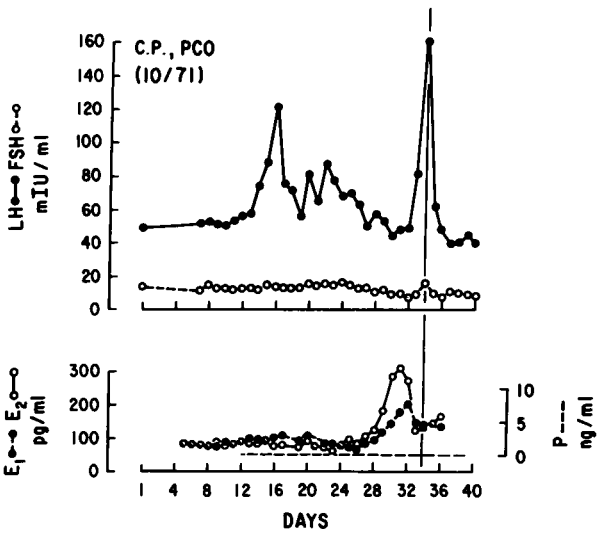

FIGURE 2 Long-term daily fluctuation of gonadotropins, E_2, E_1, and progesterone (P) levels in a PCO patient studied for 34 days.

In 25 of the 34 daily samples this latter patient's LH level was below 25 mIU/ml. Mean FSH levels were again normal. The long-term fluctuations of gonadotropins were unusually large for LH and relatively stable for FSH. Not infrequently, the magnitude of the day-to-day LH fluctuations resembled that of the midcycle LH surge. An example is depicted in Fig. 2. In this case, a surge-like LH-FSH fluctuation occurred with LH rising from 49 to 160 mIU/ml. This large LH release was preceded by a rapid increase in serum E_1 and E_2 concentrations similar to the preovulatory estrogen rise during the normal cycle. However, in this patient ovulation was judged not to have occurred because of persistently low progesterone levels.

Fig. 3 shows the effect of the E_2 infusion on LH and FSH levels in the four patients studied. Again, preinfusion LH levels were greater than 25 mIU/ml in three of the four subjects, while FSH levels were normal in all. The E_2 infusion resulted in a rapid decline in circulating LH with an attenuation of the amplitude of the pulses. The maximal decrease occurred 1–2 h after cessation of the infusions. The pattern of recovery was composed of a resumption or an exaggeration in the amplitude of LH

TABLE III

Long-Term Fluctuations of Gonadotropin Levels Determined in Daily Samples for 16–34 Days in Four Patients with PCO

Patients	Duration of sampling	Serum LH				Serum FSH	
		Mean	Coefficient of variation	Range		Mean	Coefficient of variation
				Low	High		
	days	*mIU/ml*	%	*mIU/ml*		*mIU/ml*	%
1. E. A.	34	24.1	101.3	9.5	131.0	8.9	30.8
2. J. B. S.	31	39.3	12.7	29.5	45.8	12.4	7.4
3. T. N.	16	54.9	10.5	42.8	63.7	12.4	7.4
4. C. P.	32	65.2	34.8	39.5	150.0	12.4	19.3
Mean	28.8	45.9	39.8	30.3	97.6	11.5	16.2
±SE	4.1	9.0	21.2	7.5	25.3	0.89	5.6

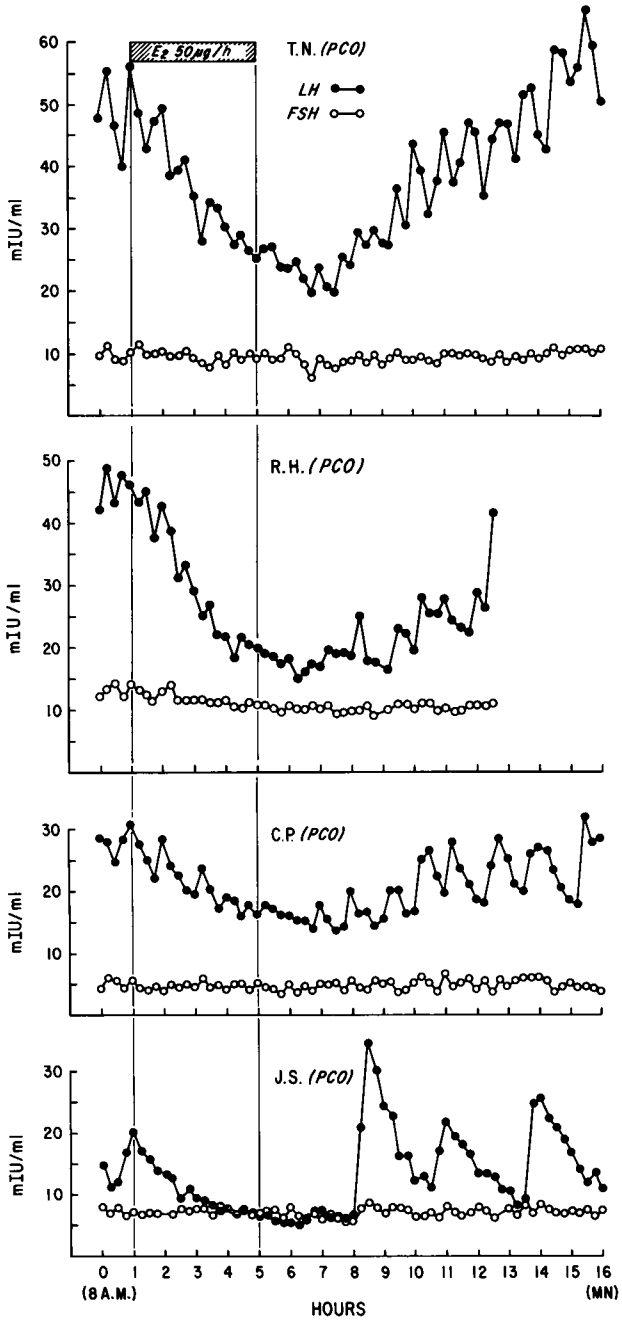

FIGURE 3 The negative-feedback effect of E_2 infusion (50 μg/h for 4 h) on the pulsatile release and the decline of basal concentrations of LH. No FSH changes were noted.

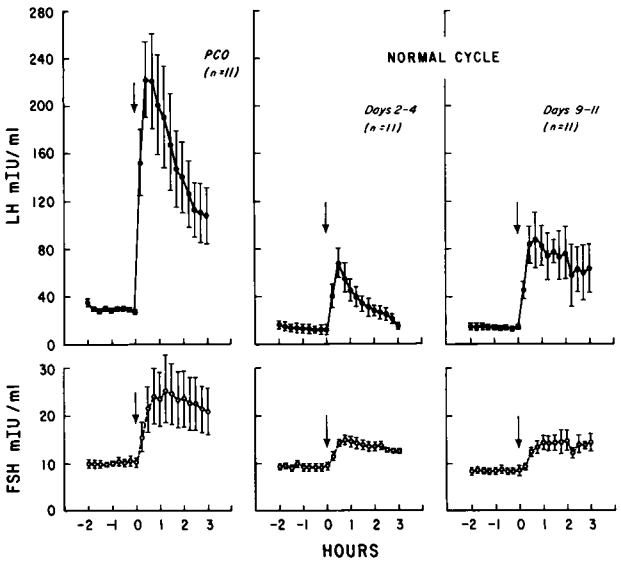

FIGURE 4 Comparison of quantitative LH and FSH release in response to a single bolus of 150 μg of LRF in PCO patients and in normal women during the early and late follicular portions of their cycle (mean±SE).

pulses. There was no clear change in FSH levels either during or after the infusions in any of the patients.

Fig. 4 shows the response of serum LH and FSH to 150-μg LRF injections in the PCO patients and normal subjects. In both groups LRF induced a prompt release of gonadotropins with the maximal rise observed at a median time of 30 min for LH (range 15–75 min) and 75 min for FSH (range 30–150 min). The net LH increase was significantly greater in PCO patients (212± 37.8 mIU/ml) than in the normal women during either the early (25.7±5.2 mIU/ml) ($P < 0.001$) or the late (54.4±7.0 mIU/ml) ($P < 0.001$) follicular phases of their cycles. The increment of FSH was also significantly greater ($P < 0.001$) in the patients with PCO (16.6±6.2 mIU/ml) than those found in the normal women either early (4.1±0.4 mIU/ml) or late (5.8± 0.8 mIU/ml) in their follicular phases. The approximated rates of decline (half-life) of LH (via semilogarithmic plot of concentration vs. time) in the PCO patients (109±21 min) was in between those calculated for the late follicular phase (190±48 min) and the early follicular phase (80±11.7 min), but these differences were not significant. Thus, the cumulative response of LH during the 3 h after the LRF injections was significantly greater in the PCO patients (7.41±1.76 IU/ml·h) than in the normal women during either the early (0.76±0.13 IU/ml·h, $P < 0.01$) or late (2.06± 0.29 IU/ml·h, $P < 0.05$) follicular phases (Fig. 5). The cumulative secretion of FSH was also significantly greater ($P < 0.05$) in the PCO patients (726.8±289.0 mIU/ml·h) than in the normal women during the early (125.3±19.4 mIU/ml·h) but not the late (182.7±48.1 mIU/ml·h) follicular phases (Fig. 5).

The regression analysis of both the ΔLH and the integrated LH response to LRF with the mean preinjection LH concentrations showed positive correlations

(Fig. 6*a*). Positive correlations were also found between the basal concentrations of E_1 and E_2 and both the ΔLH response (E_1, $P < 0.025$; E_2, $P < 0.02$) (Fig. 6*b*) and the integrated LH response to LRF (E_1, $P < 0.01$; E_2, $P < 0.05$) in the same patients. However, the real significance of E_2 on the LH response to LRF cannot be firmly established since these regression analyses are influenced by a single data point with the highest E_2 levels.

Responses to repeated 10-μg injections (five times) at 2-h intervals (pulses of LRF) in two patients are shown in Fig. 7. The net LH increases induced by the first bolus of LRF were 159 mIU/ml for T. N. and 162 mIU/ml for J. S. These were similar in magnitude to the increases induced with the larger doses of LRF (150 μg) in the other PCO patients. In response to the subsequent injections, the net and percent increase of LH decreased progressively. None of the LRF injections had a discernible effect on FSH concentrations in either subject.

Fig. 8 shows the effect of clomiphene treatment on daily LH, FSH, E_2, and progesterone levels in four PCO patients and four normal women. In response to the clomiphene treatment, the rises of circulating LH and FSH were quantitatively and qualitatively similar in the PCO patients to those found in the normal cycling women. In the PCO patients, the associated increase in serum E_2 levels was comparable to that seen during the course of normal follicular maturation (32). However, in normal cycling women the addition of the clomiphene resulted in a two- to threefold greater elevation in E_2 levels (32). The positive-feedback effect of the rise of endogenous E_2 induced an appropriate gonadotropin surge with a mean time-course of 7 days (range 5–12 days) after the completion of clomiphene treatments for both the PCO and normal subjects. These were followed by normal luteal phase rises of E_2 and progesterone, suggesting ovulation occurred in all subjects of both groups.

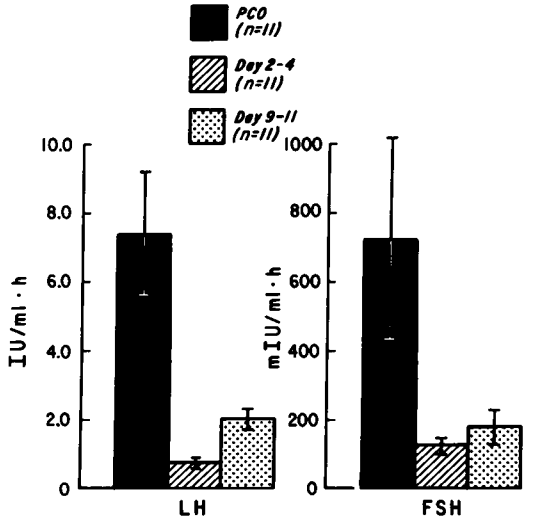

FIGURE 5 Comparison of cumulative responses (3 h) of LH and FSH release to 150 μg of LRF in PCO patients and in normal women during the early and late follicular portions of their cycle.

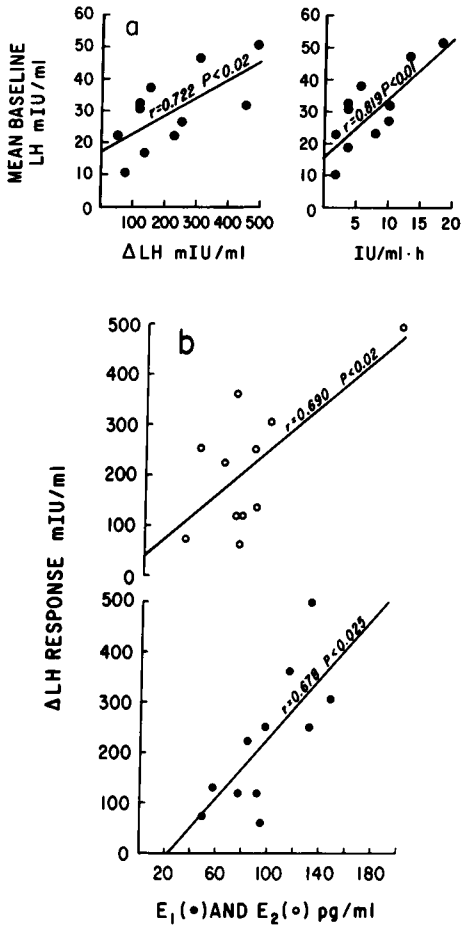

FIGURE 6 (*a*) In 11 PCO patients both the peak increments and cumulative response of LH to 150 μg of LRF correlate with the mean preinjection LH levels. (*b*) Basal E_1 and E_2 levels are positively correlated with peak increments of LH (Δ) induced by 150 μg of LRF in PCO patients.

DISCUSSION

The present study confirms and extends our previous finding of inappropriately elevated LH release and low FSH secretion in most patients with PCO syndrome (12, 13, 30). The high circulating LH levels appear to be maintained by and temporally related to exaggerations of the pulsatile discharge of LH (Fig. 1), either

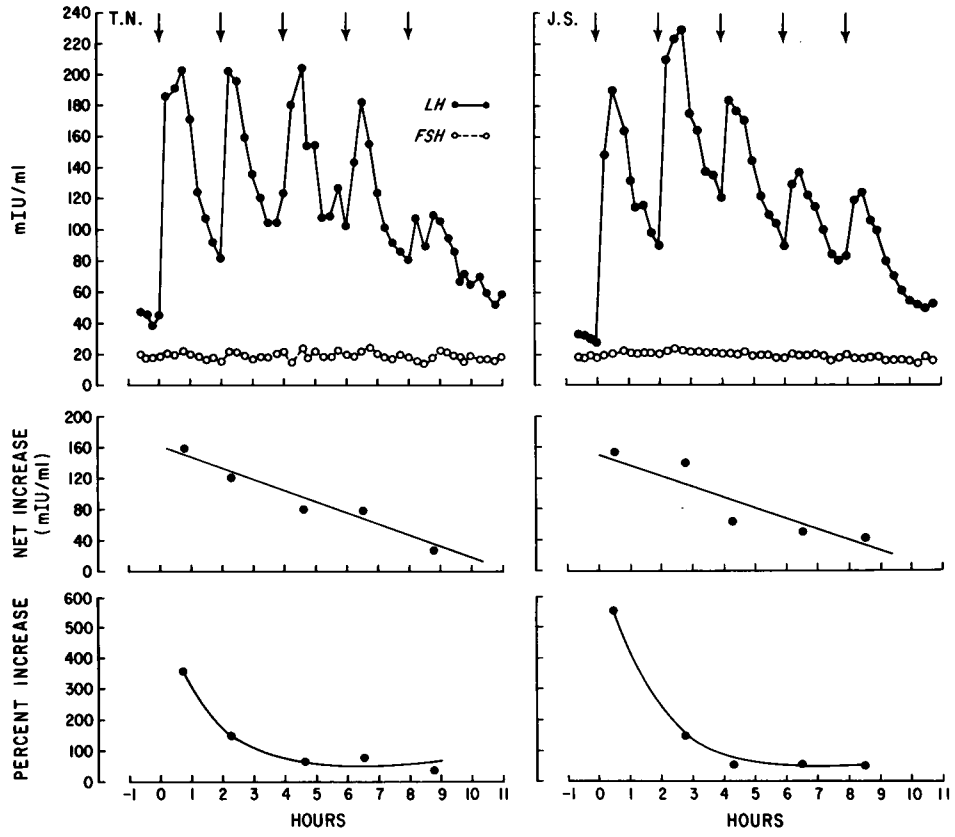

FIGURE 7 Changes in the serum concentrations, the net increase, and the percent increments of LH and FSH in response to pulses of LRF (10 μg) at 2-h intervals.

in the form of enhanced amplitude or increased frequency (oscillations). This preferentially augmented LH release exhibits marked day-to-day variation in a random fashion. Alternating periods of secretion were seen, which at times resulted in LH levels that were comparable to those seen in normally cycling women and which on other occasions were responsible for concentrations which were similar to those observed in postmenopausal women (23). In PCO patients who have been sampled either randomly or daily for up to 14 days, LH levels have been found to be elevated above the normal range for ovulatory women (except midcycle surge) in 42–73% (12–13, 30, 33–35). In patients sampled frequently for 2 days, Berger et al. (35) found that LH levels were elevated only in patients who had enlarged polycystic ovaries and not in women with normal sized gonads. Based on these findings, these authors suggested that PCO patients with normal LH levels may represent a separate group of patients. In the present subjects no relationship was noted between the size of the ovaries and concentration of LH. In the patients sampled daily the marked day-to-day variation with LH levels oscillating from the normal to elevated range (patient E. A.) suggests that patients with normal LH levels are women who were studied during a period of reduced pituitary secretion of LH and are not a distinct group. Further studies are needed to clarify this point.

That the high LH levels are not the result of a defect in the normal negative feedback of estrogen on gonadotropin release was suggested by two experiments. Firstly, the 50-μg/h E_2 infusions resulted in an acute reduction of base-line levels and attenuation of pulses of LH (Fig. 3). As reported earlier (23) this quantity of estrogen infusion results in circulating E_2 levels which vary between 300 and 800 pg/ml (a concentration comparable to the levels seen in normal women during the late follicular phase of the cycle). In these PCO patients, the response of LH to this dose of E_2 was similar to the ones observed in normal cycling women and in hypogonadal subjects (23, 25). Secondly, the administration of the antiestrogen clomiphene resulted in similar qualitative and quantitative rises of LH and FSH in both PCO patients and normal controls, presumably, through competition of the clomiphene with endogenous

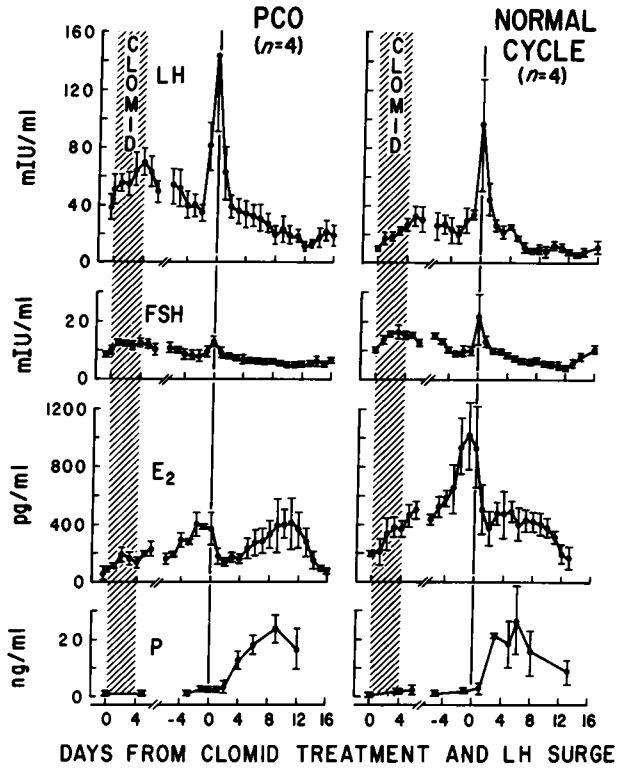

FIGURE 8 The effects of clomiphene (100 mg/day for 5 days) on the release of gonadotropins and associated changes in ovarian steroids in four PCO patients as contrasted to four normal women receiving the same treatment during the early follicular phase of their cycles (mean±SE). P, progesterone.

estrogens for binding sites in the hypothalamus and pituitary (Fig. 8).

The clomiphene study also provided evidence that the positive-feedback mechanism of estrogen on LH release was intact. The preovulatory rises of E_2 were followed by similar midcycle LH peaks in the PCO patients and normal women.

The elevated LH release appears to be related to an increase in the responsiveness of the pituitary to LRF stimulation. In response to 150 μg LRF stimulation, the net increase and the integrated release for LH and the net increase for FSH were several times greater in patients with PCO as compared to the responses seen in women during the low and high estrogen phases of the normal cycle (Figs. 4 and 5). Similar findings have been observed previously by one laboratory in PCO patients with high LH levels (34), while less consistent results have been reported by another (36). In the present patients, the increased pituitary sensitivity to LRF was particularly apparent in the smaller dose study (Fig. 7). The first bolus of LRF (10 μg) induced a response of LH release which was four times greater than the ones seen in normal women during the early follicular phase (37) and was comparable to the responses which occurred in the other PCO patients given the larger (150 μg) LRF injections. This suggests that in these PCO patients near maximal LH release occurred even at the lower dose, whereas in normal women 150 μg of LRF is necessary for maximal LH release (26).

In the present study there was a progressive decrease in pituitary responses to repeated pulses of LRF stimulation. This may reflect a depletion of pituitary gonadotropin stores, occasioned by the enhanced release as a consequence of the increase in pituitary sensitivity. Thus, the pituitary reserve when viewed as the availability of releasable LH pool may actually be increased in these patients. These interpretations are derived from observations made in identical experiments in normal women during the early and mid follicular phases of the cycle where the sensitivity is much lower and LH increments in response to successive pulses of LRF are found to be stable (38, 39).

This demonstration of a heightened pituitary sensitivity to LRF (Figs. 4, 5, and 7) offers sufficient explanation for the occurrence of the exaggerated pulsatile LH release in this syndrome without implicating an associated increase in endogenous LRF secretion. However, the possibility that increased LRF is responsible cannot be dismissed until measurements of this hypothalamic hormone are made in the portal vein blood of patients with this syndrome.

That the heightened pituitary sensitivity to LRF is responsible for the increased circulating levels of LH was suggested by the positive correlation of both the peak increments and cumulative response of LH to 150 μg of LRF with the mean preinjection LH levels. In other words, the circulating concentrations of LH closely mirrored the sensitivity of the pituitary to the LRF-mediated release of LH.

This increased pituitary sensitivity to LRF may be related to the chronically inappropriate estrogen levels (Fig. 2) found in these patients (30). A positive correlation between E_1 and E_2 levels and the basal LH concentration has been reported by us previously (30). In the present study, a significant correlation between E_1 and LH increments to LRF was also found (Fig. 6*b*). The questionable correlation between E_2 and LH increments (to LRF) need not detract from the implication of a temporally related event of the increased pituitary sensitivity and chronically inappropriate estrogen levels, since the duration of estrogen exposure is likely more important than the dose in determining the pituitary gonadotrophic activity (37). However, the possibility of a modulating role of E_1 independent of E_2 on the pituitary may exist and remains to be delineated. The

recent demonstration that the pituitary sensitivity to LRF is amplified during the late follicular phase and that it can be augmented by estrogen administration in normal and hypogonadal women (37–44) offers direct support for an estrogen-induced, high pituitary sensitivity in PCO patients resulting in an altered feedback "set point." Siiteri and MacDonald have demonstrated in patients with this syndrome that more than half of the E_1 production is derived from peripheral conversion of excessive amounts of androstenedione and that the percent conversion is related to body weight (45). These investigators have speculated that this extraglandular source of estrogen may be etiologically important in the maintenance of chronic anovulation. Our data in this and a previous publication (30) provide evidence for such causal relationships.

The disparity between LH and FSH levels in these patients may be explained by two factors. Firstly, the inhibitory feedback action of estrogen is preferential for FSH in comparison to LH (40). In the PCO patients, this preferential inhibitory action of estrogen on FSH was shown by the E_2 infusion study which resulted in a definite fall of LH but not FSH. This suggested that endogenous estrogen production was capable of sufficient negative feedback on FSH so that a large-dose, short-time infusion of exogenous estrogen could not lower FSH secretion further. This type of estrogen administration has resulted in a fall of FSH concentration in hypogonadal but not in normal cycling women (23, 25). Secondly, FSH release is relatively insensitive to LRF stimulation in comparison to LH secretion (38). This relative insensitivity of FSH release to LRF was particularly apparent in the lower dose study, where 10 μg injections stimulated large rises of LH but had no discernible effect on FSH concentrations in either patient. One other mechanism should also be considered. It is possible that polycystic ovaries may secrete some other substance such as "inhibin" that would preferentially inhibit the release of FSH.

In summary, we have presented a series of experiments to gain quantitative and qualitative information concerning the hypothalamic-pituitary function in PCO patients. Our findings suggest that the abnormal gonadotropin secretion seen in these patients is not due to an inherent defect of the hypothalamic-pituitary system but is the result of a functional derangement consequent to chronic inappropriate estrogen feedback. Based on these observations, it would appear that a vicious cycle is present which perpetuates chronic anovulation; high levels of LH stimulate the ovary to secrete increasing amounts of androgens. These androgens, particularly androstenedione, are converted to estrogens, which in turn, augment the pituitary sensitivity to endogenous LRF; and this results in an exaggerated pulsatile LH secretion and in the maintenance of an inappropriately elevated circulating LH. The low FSH secretion may be explained by the preferential inhibitory action of estrogen on FSH release, coupled with a relative insensitivity of FSH release to LRF stimulation. Ovarian factors, other than estrogen, may also be responsible for low normal FSH secretion. These findings offer an explanation for the perpetuation of chronic anovulation in patients with established PCO. They do not provide information concerning the primary etiology of this condition. Studies are currently being performed to delineate this mechanism.

ACKNOWLEDGMENTS

We are grateful for the gifts of synthetic LRF from Dr. R. Guillemin. We are indebted to T. Vargo, J. Aurand, G. Brink, N. Czekala, G. Laughlin, R. Stewart, and J. O'Toole for their skillful technical assistance. We are also grateful for the generous gifts of reagents for the LH and FSH assays from the National Pituitary Agency and the National Institute of Arthritis and Metabolic Diseases.

This work was supported by The Rockefeller Foundation (RF 75029).

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