JCI The Journal of Clinical Investigation

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J Clin Invest. 1971;50(5):1149-1153. https://doi.org/10.1172/JCI106587.

Research Article

The sequential changes in the concentration and pattern of circulating luteinizing hormone (LH) and follicle-stimulating hormone (FSH)[1] following bilateral ovariectomy were determined in 10 premenopausal women. The initial (1st wk) and delayed (3 wk) secretory responses of serum LH and FSH as related to the phases of the menstrual cycle were examined. Ovariectomy during follicular phase was accompanied by a prompt and much greater rise in both LH and FSH during the 1st wk. This rapid rise was followed by a transient decline between the 7th and 10th day which resulted in a biphasic pattern. In contrast, a slower and progressive rise in serum LH and FSH was observed in subjects ovariectomized during luteal phase of the cycle. The quantitative secretion (area under the curve) during the 1st wk after ovariectomy was significantly greater in patients operated on during the follicular phase than during the luteal phase for both LH ($P < 0.05$) and FSH ($P < 0.01$). Thereafter, a similar pattern of gonadotropin rise was observed for patients ovariectonized during either phase of the cycle and reached a plateau by the end of the 3rd wk. At this time, the mean LH concentration increased 6-fold for follicular phase surgery and 8-fold for luteal phase surgery. The mean serum FSH concentration increased 8-fold for follicular phase surgery and 12-fold for […]

The Effect of Ovariectomy on Gonadotropin Release

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ABSTRACT The sequential changes in the concentration and pattern of circulating luteinizing hormone (LH) and follicle-stimulating hormone (FSH)[1] following bilateral ovariectomy were determined in 10 premenopausal women. The initial (1st wk) and delayed (3 wk) secretory responses of serum LH and FSH as related to the phases of the menstrual cycle were examined. Ovariectomy during follicular phase was accompanied by a prompt and much greater rise in both LH and FSH during the 1st wk. This rapid rise was followed by a transient decline between the 7th and 10th day which resulted in a biphasic pattern. In contrast, a slower and progressive rise in serum LH and FSH was observed in subjects ovariectomized during luteal phase of the cycle. The quantitative secretion (area under the curve) during the 1st wk after ovariectomy was significantly greater in patients operated on during the follicular phase than during the luteal phase for both LH ($P < 0.05$) and FSH ($P < 0.01$). Thereafter, a similar pattern of gonadotropin rise was observed for patients ovariectomized during either phase of the cycle and reached a plateau by the end of the 3rd wk. At this time, the mean LH concentration increased 6-fold for follicular phase surgery and 8-fold for luteal phase surgery. The mean serum FSH concentration increased 8-fold for follicular phase surgery and 12-fold for luteal phase surgery. The net increase in serum FSH level was higher than that in the serum LH level after surgery in both phases of the cycle and thus a reversal of FSH/LH ratio occurred. These data provide indirect evidence that the phase of ovarian steroid secretion may exert a quantitative influence on the gonadotropin turnover rate within the hypothalamic-pituitary system. The augmented gonadotropin release and the reversal of FSH/LH ratio following ovariectomy presumably could be due to an increased gonadotropin net synthesis which is more pronounced for FSH than for LH.

Dr. Tsai is a Research Fellow in Reproductive Endocrinology.

Received for publication 8 October 1970 and in revised form 12 November 1970.

[1] *Abbreviations used in this paper:* LH, luteinizing hormone; FSH, follicle-stimulating hormone.

INTRODUCTION

Based on the data of metabolic clearance rate studies, the secretory rates of FSH (follicle-stimulating hormone) and LH (luteinizing hormone) are higher during the follicular phase than during the luteal phase of the ovulatory cycle (1, 2). It has been suggested that this difference in the release of pituitary gonadotropins is related to the feedback effect of ovarian steroids (3, 4). However, meaningful data on the qualitative and quantitative effects of ovarian steroids on gonadotropin release in humans are not available. Inquiry into the gonadotropin release pattern after acute interruption of ovarian steroid feedback action during the follicular and luteal phases of the cycle should provide some useful information. The present study was undertaken to delineate the sequential changes in the concentration and the pattern of circulating LH and FSH after bilateral ovariectomy in premenopausal women. The initial and delayed secretory responses of serum LH and FSH as related to the phases of the menstrual cycle were examined.

METHODS

Between the years 1966 and 1970, 10 patients volunteered for this study. Their ages ranged between 24 and 41, and all had a history of regular menstrual cycles. The length of their cycles varied from 27 to 31 days with a mean of 29 days. Bilateral ovariectomy was performed in conjunction with hysterectomy as part of the treatment for chronic pelvic inflammatory disease, endometriosis, and uterine fibroids. The patients had not received medication for at least 3 months before this procedure. Morning blood samples were obtained before and after ovariectomy for 3 wk. Daily samples were collected the first 10 days and at 3- to 5-day intervals thereafter. Serum concentrations of LH, FSH, and progesterone were determined. The data were analyzed according to the phase of the menstrual cycle which was

TABLE I
Clinical and Laboratory Data on 10 Patients before Ovariectomy

Patient No.	Initials	Age	Day of cycle at ovariectomy	Histology: Endometrium	Histology: Ovaries	Concentrations before ovariectomy: LH	FSH	Progesterone
						mIU/ml	*mIU/ml*	*ng/ml*
1	A. V.	27	2	Menstrual	NPD*	19.3	12.7	0.5
2	H. M.	35	9	Prolif.	NPD*	9.9	8.5	<0.2
3	M. P.	34	9	Prolif.	NPD*	14.6	7.6	<0.2
4	J. A.	41	10	Prolif.	Follicle cysts	12.9	8.0	<0.2
5	M. H.	32	9	Prolif.	NPD*	10.0	7.8	<0.2
6	J. B.	45	18	—	NPD*	13.0	5.5	12.0
7	H. Mc.	35	20	Secretory	NPD*	3.4	4.0	9.5
8	R. R.	36	21	Secretory	Corpus luteum cyst	6.5	3.8	5.6
9	A. M.	40	23	Secretory	NPD*	1.5	9.7	2.8
10	D. H.	24	28	Secretory	Corpus luteum	16.0	5.6	1.7

*NPD = No pathological diagnosis.

determined by endometrial and ovarian histology, and by serum progesterone concentrations (Table I). Five patients were assigned as follicular phase and five as luteal phase of the menstrual cycle at the time of ovariectomy. There were no major postoperative complications. Meperidine hydrochloride was the only medication used during the immediate postoperative period on all patients.

In order to determine the quantitative differences in the gonadotropin rise between the two phases of the menstrual cycle during the 1st wk after ovariectomy, the cumulative hormone secretion was determined by measuring the area under the curve and it was used as an index of quantitative response. The observed concentrations were connected by straight-line segments and the area under these segments was calculated by the method of triangulation. This area was expressed in arbitrary units.

The double antibody radioimmunoassay procedures for FSH and LH employed in this study were similar to those described by Midgley (5, 6). The Second International Reference Preparation of Human Menopausal Gonadotropin (2nd IRP-HMG) was used as the reference standard for both FSH and LH assay and expressed as mIU 2nd IRP-HMG/ml serum. Comparison of the relative potency of 2nd IRP-HMG and pituitary standard LER 907[2] in the radioimmunoassay systems revealed 38 mIU/μg for FSH and 210 mIU/μg for LH. The sensitivity, specificity, and precision of the assay have been reported previously (7, 8). The same antigen[1] and antibodies[1] were used in the present study. All samples of serum from a sequential study were run in the same assay in duplicate.

Competitive protein-binding assay for serum progesterone described by Murphy (9) and Neill, Johansson, Datta, and Knobil (10) has been used in this and previous studies (7, 11). This method has a coefficient of variation of 9% in the range of 0.25 to 3 ng/ml and a sensitivity of 0.1 to 0.2 ng/ml. In this study, values below 0.2 ng/ml were considered undetectable.

[2] Purified human pituitary LH (DEAE-2-2, 981 IU/mg bioassay against 2nd IRP-HMG) and HCG-antiserum were gifts from Dr. A. Parlow and Dr. A. R. Midgley, Jr., respectively. Pituitary FSH (LER 869-2), FSH antiserum (batch 1) and pituitary standard (LER 907) were kindly supplied by the National Pituitary Agency and the National Institute of Arthritis and Metabolic Diseases.

RESULTS

The serum concentrations of FSH, LH, and progesterone before ovariectomy are shown in Table I. These values are within the limit of normal for adult eugonadal women (11). The progesterone concentrations detected in patients during the luteal phase of the cycle are suggestive evidence for ovulation, and undetectable serum progesterone in subjects during follicular phase of the cycle are consistent with previous studies (4, 11).

The changes in the mean concentrations and the patterns of serum FSH and LH after ovariectomy in the two phases of the cycle during the period of 3 wk observations are shown in Fig. 1. It is apparent that ovariectomy is accompanied by a progressive rise in both gonadotropin levels, approaching a plateau by the end of the 3rd wk. There is a reversal of FSH/LH ratio to above 1 which occurred sooner when ovariectomy was performed during the luteal phase (day 2) than during the follicular phase (day 5). This ratio persisted throughout the 3 wk of observation. At the end of 3 wk of observation, the mean serum LH concentration increased 6-fold (from 14.2 $\pm$2.0 to 78.2 $\pm$7.1 mIU/ml) for patients ovariectomized during the follicular phase and 8-fold for those operated on during the luteal phase (from 8.2 $\pm$2.9 to 65.4 $\pm$6.3 mIU/ml). The mean serum FSH concentration increased 8-fold for follicular phase patients (from 9.3 $\pm$1.2 to 84 $\pm$5.2 mIU/ml) and 12-fold for luteal phase patients (from 5.7 $\pm$1.0 to 82 $\pm$6.1 mIU/ml). Thus, the net increase in the serum FSH level appeared to be higher than the serum LH level in patients operated on during both phases of the cycle.

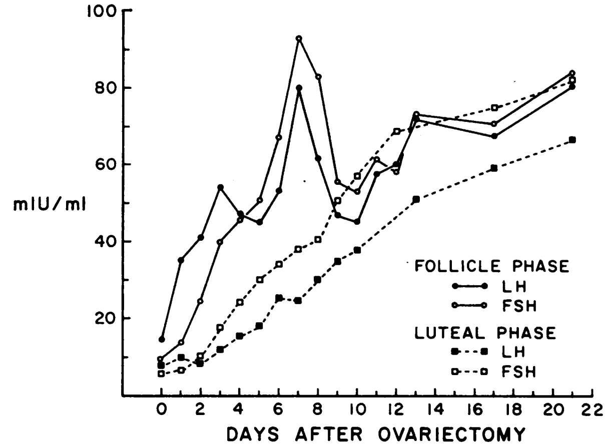

FIGURE 1 The changes in the daily mean concentrations of FSH and LH before (day 0) and following bilateral ovariectomy. The pattern of gonadotropin rise is contrasted between subjects ovariectomized during follicle phase (*N*, 5 subjects) and during luteal phase (*N*, 5 subjects) of the cycle.

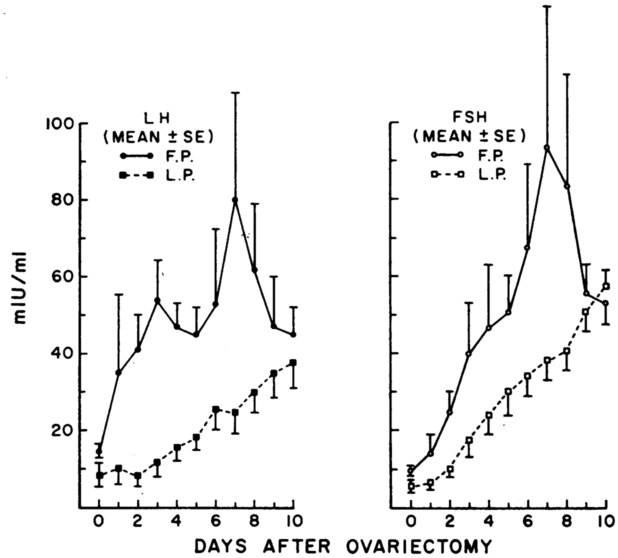

FIGURE 2 Analysis of the incremental changes of the mean (±SE) serum FSH and LH concentrations between the two phases of the cycle when ovariectomy was performed. (FP = follicle phase, LP = luteal phase). A significant higher rise of LH occurred on days 2, 3, and 4 in FP ($P < 0.05$). FSH rise was not statistically significant.

Fig. 2 shows the analysis of the initial response (first 10 days) in the incremental changes of daily FSH and LH concentrations (mean ±SE) after ovariectomy. At the end of the 1st wk after ovariectomy, there was a 5.6-fold increase for LH and 10-fold increase for FSH in patients ovariectomized during the follicle phase of the cycle. This rapid rise was followed by a transient decline between the 7th and 10th day which resulted in a biphasic pattern. In contrast, a slower and progressive rise in serum LH (3-fold) and FSH (6.6-fold) was observed in patients ovariectomized during luteal phase of the cycle. For LH, a significant rise occurred on day 2 in patients ovariectomized during follicular phase of the cycle ($P < 0.01$) but not until day 5 for patients ovariectomized during luteal phase of the cycle ($P < 0.05$). FSH, on the other hand, showed a significant rise on day 2 for both phases of the cycle ($P < 0.05$).

Comparison of daily changes in the concentrations of FSH and LH (mean ±SE) between the two phases of the cycle showed a statistically significant difference only in the LH concentrations which occurred on days 2, 3, and 4 after ovariectomy ($P < 0.05$) (Fig. 2). However, when the areas under the curves during the first 7 days were calculated, the quantitative secretion was significantly higher in patients ovariectomized during the follicular phase than during the luteal phase of the cycle for both FSH ($P < 0.01$) and LH ($P < 0.05$) (Fig. 3).

DISCUSSION

Since the metabolic clearance rate for LH (1) and FSH (2) are similar between pre- and postmenopausal women and between the follicular and the luteal phase of the cycle, it would appear that the clearance and the volume of distribution are unaffected by the presence or absence of ovarian steroids. In addition, it has been shown that stress from surgery and anesthesia does not appear to influence gonadotropin secretion (12). Thus, the observed rise in the serum gonadotropin concentrations after ovariectomy probably reflects an increased pituitary release.

In the present study, a prompt and significantly greater rise in both FSH and LH during the initial phase after ovariectomy was observed in pre- than in postovulatory subjects (Figs. 1–3). These data provide indirect evidence that the phases of ovarian steroid secretion may exert a quantitative influence in the gonadotropin turn-

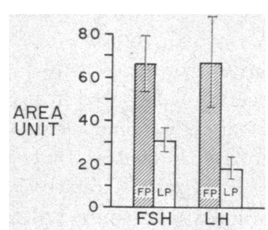

FIGURE 3 The quantitative secretion (area under the curve) of FSH and LH during the 1st wk after ovariectomy (FP = follicle phase, LP = luteal phase). A significantly greater release of FSH ($P < 0.01$) and LH ($P < 0.05$) was observed in subjects ovariectomized during FP than during LP of the cycle (mean ±SE).

over rates within the hypothalamic-pituitary system (synthesis, storage, and release). It is possible that estrogen (follicular phase) may induce an increased synthesis which exceeds the rate of release of both FSH and LH. Thus, a net increase in the pituitary store coupled with the preexisting increased synthesis may account for the rapid rate of release seen in the initial phase after acute ovarian ablation. During luteal phase of the cycle, the presence of estrogen and progesterone may exert an effect of reduced synthesis as well as inhibit the release. Hence, a slower pituitary turnover rate of both FSH and LH may be responsible for the relatively slower rise in gonadotropin levels seen in postovulatory subjects in response to ovariectomy. This is consistent with the finding that serum FSH and LH levels are significantly lower in the luteal phase of the cycle than in the follicular phase of the cycle (4, 11). Since data concerning the fluctuation of pituitary gonadotropin concentrations during various stages of the menstrual cycle are not available, explanations to account for our present findings must be regarded as speculative. However, several experimental data obtained in rats are relevant to the present findings and may lend some support to the above discussion. Barraclough and Haller (13) have shown that in ovariectomized rats, a moderate amount of estrogen induced an increased pituitary synthesis and storage of LH without changes in the releasing mechanism. Gay and Bogdanove (14) have shown that estrogen plus progesterone treatment in castrated rats resulted in a decrease in plasma FSH and LH levels without altering pituitary concentrations, implying a decrease in the net synthesis.

After the initial phase, a similar progressive rise in gonadotropin levels was noted in both phases of the cycle (Fig. 1). This suggests that the increased synthesis and release have reached a comparable rate. After ovariectomy, a reversal of FSH/LH ratio to above 1 was observed. The relative longer half-life for FSH (8) than LH (15) may influence the shape of gonadotropin curve initially, but the reversal of FSH/LH ratio was principally reflecting a higher secretory rate for FSH than for LH. This is consistent with the metabolic clearance rate studies (1, 2) which indicate a more than 10-fold increase in the daily production rate for FSH but only 3- to 4-fold increase for LH between pre- and postmenopausal women. Limited evidence available on pituitary gonadotropin content indicates that an approximate 3-fold increase in FSH with a relatively unchanged LH content is found in post- as compared to premenopausal women (16). By inference, the increased release of FSH and LH after ovariectomy is associated with an increased net synthesis which is more pronounced for FSH than for LH. The delayed change in reversal of FSH/LH ratio observed in follicular phase (5 days) as compared to the luteal phase (2 days) is related solely to the more pronounced LH increments in response to ovariectomy in preovulatory subjects. These data suggest that the ovary exerts more inhibitory action on the release and synthesis of FSH than LH. Recently, Gay and Midgley (17) and Yamamoto, Diebel, and Bogdanove (18) by analysis of concomitant changes in the serum and pituitary LH levels, have shown that the augmented LH release was soon followed by the net increase in LH synthesis in response to ovariectomy in adult rats. Although these data have provided information about the complex interactions between gonadotropin synthesis, release, and ovarian steroids, the precise mechanism responsible for the observed relationships has yet to be established.

ACKNOWLEDGMENTS

This work was supported in part by grants from American Cancer Society (T-504), Pardee Foundation, and Ford Foundation.

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