Hormonal Characteristics of the Human Menstrual Cycle throughout Reproductive Life

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ABSTRACT The changes in serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, and progesterone that occur both early and late in reproductive life were characterized and compared with findings in young, normal women and in patients with certain menstrual disorders.

A total of 50 complete menstrual cycles in 37 women were examined. Five distinct patterns of hormonal regulation were found, three of which are reported here: (*a*) A long follicular phase and delayed follicular maturation in young women with long, unpredictable intermenstrual intervals from menarche; (*b*) a short follicular phase with increasing age and in short cycles in perimenopausal women; and (*c*) true anovulatory vaginal bleeding in long cycles in perimenopausal women.

The short cycles before and during the menopausal transition were found to have lower E_2 levels and high FSH concentrations throughout, while LH remained in the normal range. During long cycles in perimenopausal women, concentrations of LH and FSH were in the menopausal range. However, follicular maturation was observed months after high levels of gonadotropins were attained.

These studies permit the characterization of the menstrual history of the normal woman in terms of the hormonal changes that occur and provide a basis for the definition of several disorders of follicular maturation.

INTRODUCTION

Irregular patterns of menstruation are common in some women at all times of reproductive life. In large populations studied prospectively, variability in cycle length has been shown during the years that immediately follow menarche and precede menopause (1). The pattern of vaginal bleeding after menarche is often characterized by long intermenstrual intervals. Between the ages of 25 and 40, cycle length is regular, and there is a gradual decrease in total cycle length until the menopausal transition. Before menopause, the pattern of vaginal bleeding again becomes irregular, long intervals, often alternating with unusually short cycles (1).

Analysis of hormonal regulation of the human menstrual cycle by measurement of circulating pituitary and ovarian hormones has, to date, been limited to young women with regular cycle (2–10) or to clinically abnormal cycles (11–17). We have measured serum levels of serum luteinizing hormone (LH),[1] follicle-stimulating hormone (FSH), estradiol (E_2), and progesterone (P), throughout the cycles of women at the extremes of menstrual experience and compared the findings with those in young and middle-aged normal women and in certain menstrual disorders previously reported (16, 17).

Long cycles in young women of normal body weight were characterized by delayed follicular maturation and hormonal changes suggesting normal ovulation. In older women, decreased cycle length was due to a short follicular phase. In regularly menstruating premenopausal women there was hormonal evidence of follicular maturation and corpus luteum function with a significant decrease in length of the follicular phase, diminished E_2 concentrations, and striking increases in the concentration of FSH throughout the cycle. During long cycles in perimenopausal women, levels of LH and FSH were in the menopausal range and vaginal bleeding occurred in the absence of follicular maturation

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[1] *Abbreviations used in this paper:* E_2, estradiol; FSH, follicle-stimulating hormone; LH, luteinizing hormone; P, progesterone.

or after follicular maturation and subnormal corpus luteum P secretion. In one individual, long, anovulatory cycles were followed by a short cycle showing fluctuations in hormone levels characteristic of follicular maturation and corpus luteum formation.

These findings provide endocrine correlations to epidemiologic observations of menstrual cycle length throughout reproductive life (1). Early variability in cycle length appears to be due to delayed follicular maturation. The general decrease in cycle length in later reproductive life is attributable to a shorter follicular phase, which in premenopausal women is accompanied by a striking increase in FSH and significantly decreased E_2 levels throughout the cycle. The variable pattern of vaginal bleeding that may occur during the menopausal transition is, like the menarchial transition, attributable to irregular follicular maturation. Very short cycles, associated with hormonal changes characteristic of follicular maturation, are interspersed among unusually long cycles that show no signs of corpus luteum formation.

METHODS

Subjects. Students in the College of Nursing, nurses, employees of University Hospital, and patients of the Endocrinology Clinic were asked to serve as paid volunteers for studies of homonal correlations of the menstrual cycle. A detailed menstrual history was obtained, and blood samples were obtained daily on an outpatient basis during at least one complete cycle. Each subject was maintained on ferrous sulfate, experienced no reduction of hematocrit, and pursued normal activities during the study.

10 subjects, age 18–30, with histories of regular menstruation, who had cycles demonstrating an early follicular phase increase in FSH, a preovulatory LH peak, a luteal phase of at least 11 days, a luteal phase P peak greater than 10 ng/ml, and a biphasic basal body temperature record, constituted the reference group. 16 women who had blood drawn during a total of 19 cycles constituted the experimental group. They could be divided into four categories.

(*a*) One cycle was studied in each of four normal-weight subjects, age 18–21, who gave histories of long intermenstrual intervals from time of menarche. (*b*) One cycle was examined in each of five women, age 40–41, with histories of regular menses. Three were parous, and two were nulliparous. (*c*) Six cycles were examined in six women, age 46–51, who had regular menses and no menopausal symp-

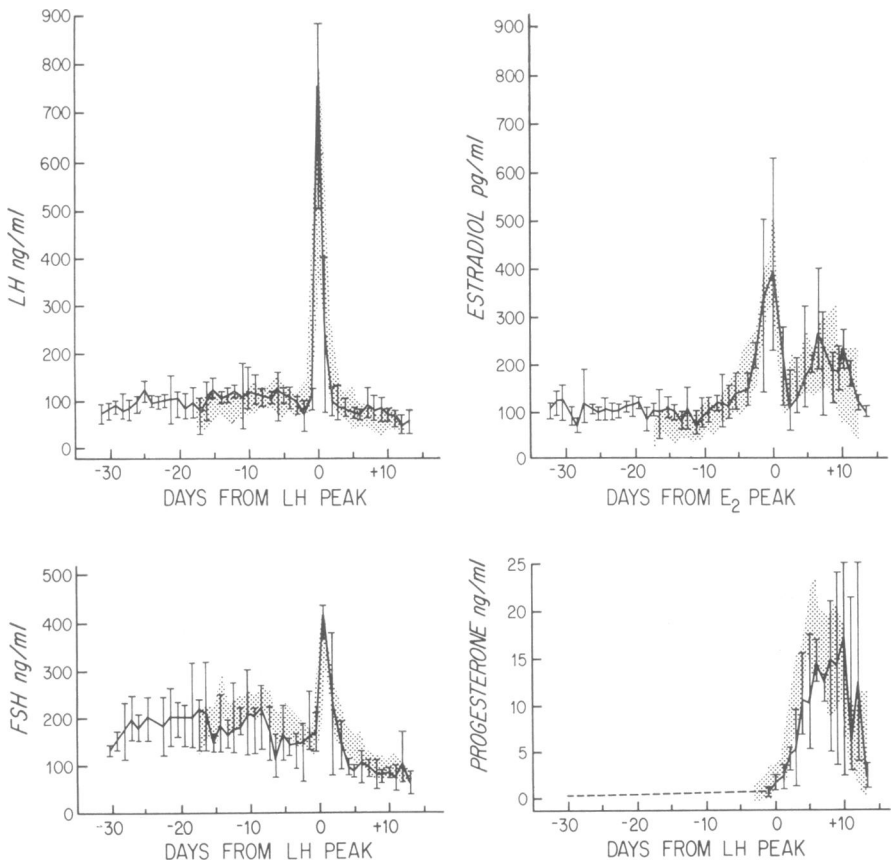

FIGURE 1 The mean and range of serum LH, FSH, E_2, and P in four women, age 18–21, with infrequent menses are compared with the mean±2 SEM in 10 cycles in women age 18–30 (shaded area). LH, FSH, and P levels are synchronized around the day of the LH peak, and E_2 levels are synchronized around the day of the E_2 peak.

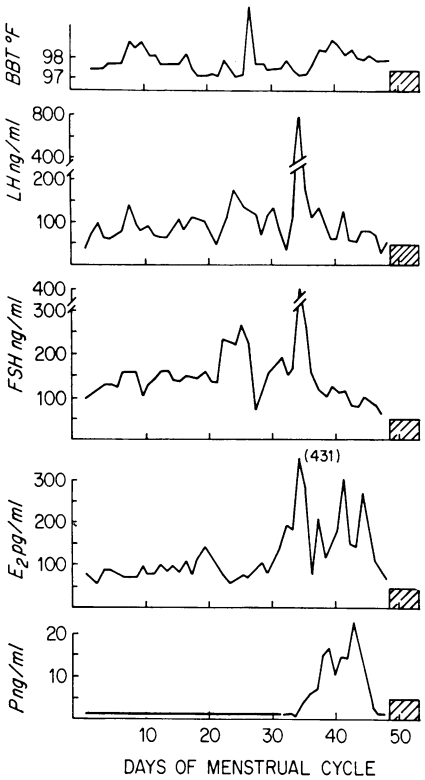

FIGURE 2 Daily concentrations of serum LH, FSH, E_2, and P and basal body temperature (BBT) in one subject, age 19, with infrequent menses. The cycle is synchronized around the day of the LH peak. The hatched area indicates menstruation.

toms. Three were aware that cycle length had decreased in recent years. Four were parous, and two were nulliparous (4). In one of these women, hormone analysis was carried out during the last 54 days of a subsequent cycle of more than 3 mo duration. Another woman, age 49, maintained a menstrual calendar from age 40. Long cycle intervals, unaccompanied by menopausal symptoms, began at age 48. Homone analysis was done during cycles of 63, 53, and 27 days.

Methods. Serum was stored at −20°C, and each cycle was assayed as a unit so that fluctuations would represent intra- rather than interassay variation. The serum FSH and LH were measured by radioimmunoassay in a standard double-antibody system utilizing reagents supplied by the National Pituitary Agency (18, 19). Results were expressed as nanograms per milliliter of the reference preparation LER 907. P and E_2 were measured with antisera generously supplied by Dr. Gordon Niswender, and activated charcoal was used to separate bound from free steroid. The E_2 method employed a specific antiserum and a simple ether extraction of serum (20).

RESULTS

The values for LH, FSH, E_2, and P in 10 women, age 18–30, shown in the shaded area of Figs. 1, 3, and 4, were not different from those described by others for women in this age group (2–9). In each instance FSH, LH, and P secretion were oriented with regard to the LH peak, designated day 0. E_2 values were oriented by the E_2 peak because of the known variability in the relationship between the E_2 and LH peaks (10).

In each of the experimental groups the mean and range of values for each day are compared with the reference population. It must be emphasized that the range given encompasses a group of cycles and that in

TABLE I

Characteristics of Menstrual Cycle Length in Normal Women throughout Reproductive Life and in Disorders of Follicular Maturation

Group	Follicular phase‡	Luteal phase§	Total cycle length
	days	*days*	*days*
Age 18–30	16.9±3.7	12.9±1.8	30.0±3.6
Age 40–41	10.4±2.9	15.0±0.9	25.4±2.3
Age 46–51	8.16±2.8*	15.9±1.3	23.2±2.9
Long follicular phase	33.0±2.2	14.2±2.2	47.2±4.3
Short luteal phase	17.2±1.7	7.0±2.4*	24.2±3.6
Inadequate luteal phase	71.6±50.5*	12.3±0.5	84.0±50.6*

Results are means ±SD.
* $P = < 0.05$.
‡ Follicular phase is from first day of menses to the LH peak.
§ Luteal phase is from LH peak to onset of menses.

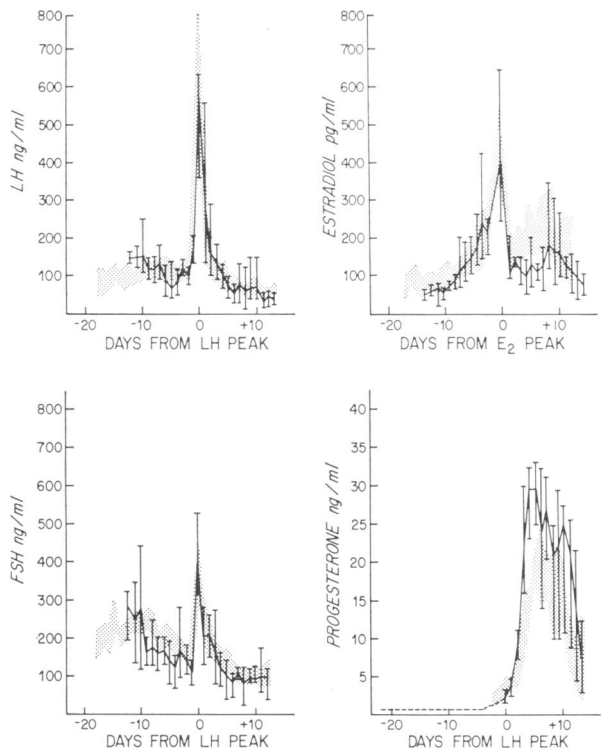

FIGURE 3 The mean and range of serum LH, FSH, E_2, and P in five women, age 40–41, are compared to the mean ±2 SEM in 10 cycles in women aged 18–30. The data are illustrated as in Fig. 1.

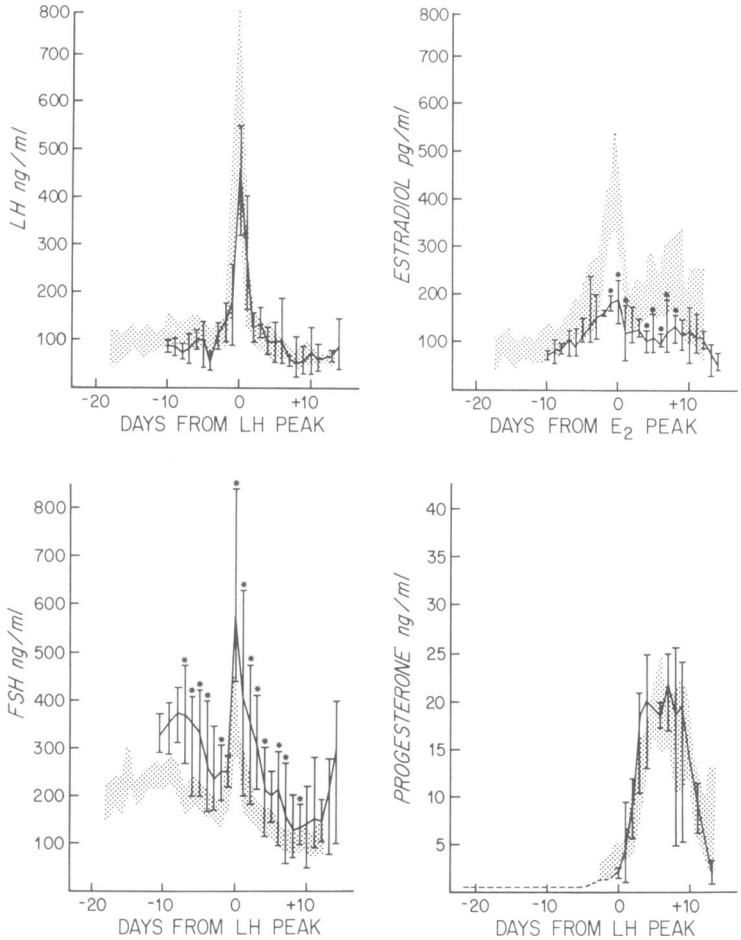

FIGURE 4 The mean and range of serum LH, FSH, E_2, and P in six premenopausal women with regular menses are compared with the mean±2 SEM in 10 cycles in women aged 18–30. The data are illustrated as in Fig. 1. An asterisk (*) indicates a statistically significant difference between the values of the two groups, $P = < 0.05$.

no case were a series of extreme values, high or low, derived from a single patient.

The mean and range of hormone values in four long cycles obtained from four normal-weight women, age 18–21, with infrequent menstruation from the time of menarche, are shown in Fig. 1. In each case an indeterminately long follicular phase was followed by changes in hormone concentrations indicative of follicular maturation, ovulation, and corpus luteum function identical to those observed in the normal cycles. The increased cycle length was always due to a prolonged follicular phase of the cycle as measured by the time before the LH peak (Table I). During the prolonged follicular phase, E_2 levels were 70–110 pg/ml, LH and FSH were in the range observed during the normal follicular phase, and P was less than 1 ng/ml. In two of these cycles the maturation of a follicle was preceded by a rise of FSH comparable to that seen during the early follicular phase of many normal-length cycles. This increase in FSH occurred during days 20–25 of the cycle illustrated in Fig. 2. The FSH rise was not sustained and, as in the normal group, fell slightly with follicular maturation.

In the women age 40–41, hormone values did not differ from those observed in the younger subjects (Fig. 3). The decrease in mean cycle length (25.4 days) compared to the younger women (30.0 days) was attributable to a shorter interval between the onset of menses and the LH peak. The duration of time necessary for the follicle to complete its maturation, as characterized by the exponential rise in estradiol secretion, was no different in the two groups.

The six premenopausal women, age 46–51, had cycles shorter in total length (mean 23.3 days) than women 18–21 (Table I, Fig. 4). This was attributable to a shortened follicular phase of 4–13 (mean 8.3) days. By

contrast, the luteal phase, as measured from the LH peak to the onset of menses, was 10–16 (mean 13.0) days, and P levels were not different from those observed in younger women (Fig. 4). The E_2 concentration during the early follicular phase was 70–110 pg/ml, while the mean midcycle peak, 192 pg/ml, and the mean maximal luteal phase concentration, 157 pg/ml, were significantly lower than observed in the younger women ($P = < 0.05$). It was of particular interest that the serum FSH was strikingly increased throughout the cycle, despite the attainment of levels of E_2 that might be expected to suppress its secretion, while LH remained indistinguishable from normal.

Fig. 5 illustrates the daily hormone levels during two cycles in one of the 50-yr-old subjects. When the first cycle was studied, there had been no change in the pattern of vaginal bleeding, and she demonstrated the elevated FSH levels seen in this group. Blood sampling was resumed 4 mo later during her first unusually long intermenstrual interval, and both LH and FSH were in the menopausal range. It was of note that hormonal changes associated with follicular maturation ensued even at high gonadotropin concentrations. Vaginal bleeding followed a progressive rise in E_2 and a sustained increase in serum P. The concentrations of P did not exceed 10 ng/ml, typical of the previously described inadequate luteal phase (17).

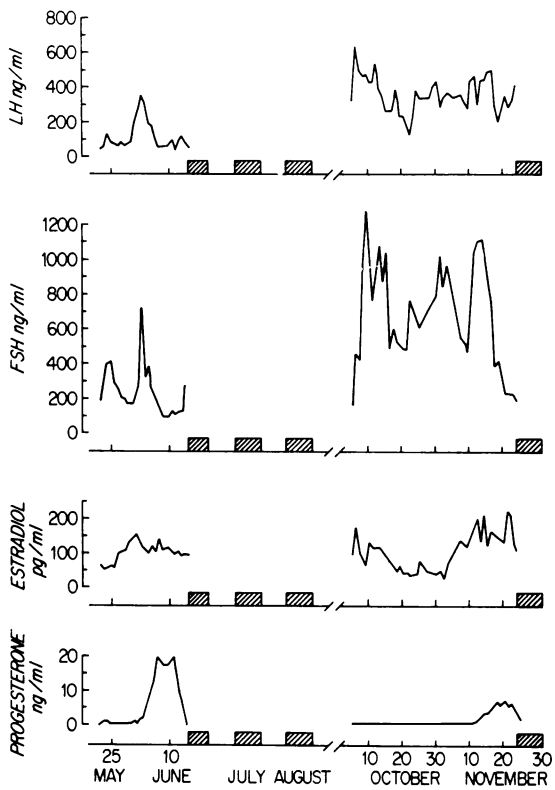

FIGURE 5 Concentrations of LH, FSH, E_2, and P during two cycles in one 50-yr-old subject. Hormone levels are arrayed by calendar date, and the hatched areas indicate menstruation.

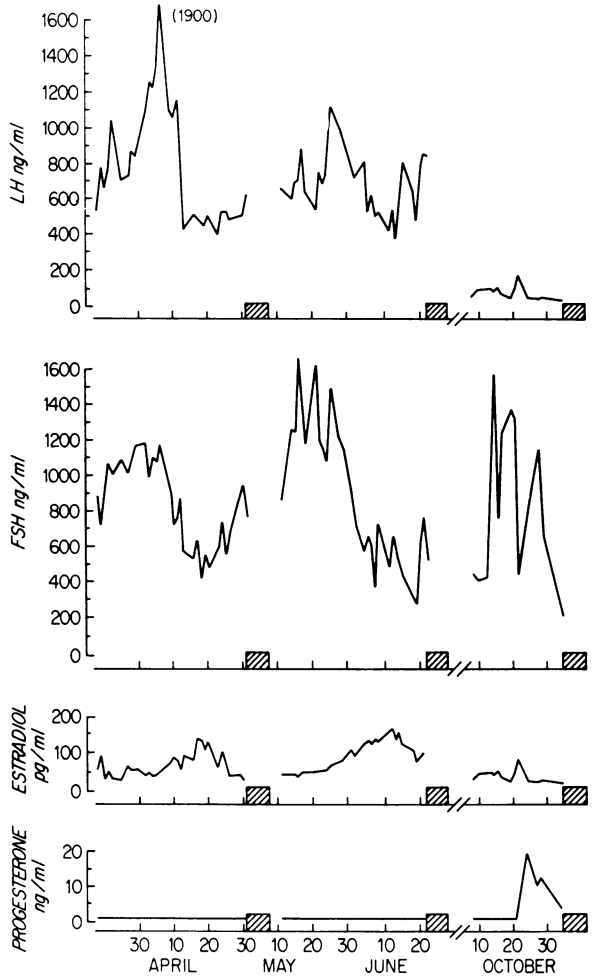

FIGURE 6 Daily concentrations of serum LH, FSH, E_2, and P during three cycles in one 49-yr-old subject. Hormone levels are arrayed by calendar date, and the hatched area indicates menstruation.

A 49–yr-old woman kept a menstrual calendar for 9 yr, during which mean cycle length was 28.0 days. She began to experience unusually long intermenstrual intervals, and studies done during cycle of 63 and 53 days showed LH and FSH levels greater than 600 ng/ml (Fig. 6). Basal E_2 levels of 30–50 pg/ml increased to peaks of 125–150 pg/ml, accompanied by reciprocal, proportionate suppression of LH and FSH. The P concentration was always less than 1 ng/ml, and vaginal bleeding occurred after a period of increased E_2 secretion. A subsequent cycle of 27 days in the same subject demonstrated evidence of follicular maturation and luteinization. The E_2 concentration increased from

less than 20 pg/ml to a maximum of 115 pg/ml at midcycle, while the P level rose from less than 1 ng/ml to 19 ng/ml during days 17–19. LH concentrations were in the normal range throughout the cycle, while FSH remained elevated, with maximum levels of 1,500 ng/ml falling to a low of 200 ng/ml at the end of the luteal phase. Thus an anovulatory cycle was followed by a cycle that demonstrated evidence of follicular maturation.

DISCUSSION

These studies were based on the monumental prospective study of menstrual cycle length reported by Treloar, Boynton, Benn, and Brown, which showed that the 5–7 yr after menarche and 6–8 yr before menopause were characterized by wide variability in cycle length and contrasted with the years from 20 to 40, during which cycle length was regular and there was a gradual decrease of 2–3 days in mean cycle length (1). We have described the endocrinologic features of menstrual cycles at the extremes of reproductive life and compared them with cycles in regularly menstruating young women and with abnormal cycles recently reported.

Long cycles during the menarchial transition were characterized by delayed but completely normal follicular maturation, including basal body temperature records (Figs. 1 and 2, Table I). Although the study of the menstrual cycles in the years immediately after menarche could not be done because of the necessity for frequent blood samples, the four young women reported here all had histories of irregular menses from the time of menarche.

In regularly menstruating women, age 40–41, the hormonal features of follicular maturation and corpus luteum function were not different from those of younger women (Fig. 3, Table I). The slightly shorter cycle length was in all cases attributable to a reduced interval between the first day of menses and the midcycle gonadotropin peak.

In contrast to the delayed follicular maturation in young women, regularly menstruating premenopausal women, age 46–51, often had short cycles also attributable in all cases to decreases in the time preceding hormonal evidence of follicular maturation. In these women, early follicular phase E_2 levels were not different from those in younger women. The lower midcycle and luteal phase E_2 concentrations must reflect decreased secretion by the maturing follicle and corpus luteum, since the metabolic clearance rate of E_2 is not different in pre- and postmenopausal women (21). This contrasts with corpus luteum P secretion, which was usually equal to that found in the younger women.

Long cycles during the menopausal transition women were terminated by an inadequate luteal phase or by an episode of vaginal bleeding that followed a simple decline in E_2 concentration without hormonal evidence of ovulation or corpus luteum formation and in the presence of menopausal levels of gonadotropins, i.e., truly anovulatory cycles. The long cycles with high gonadotropin concentrations did not necessarily indicate the absence of follicles, because at least in one instance a short cycle demonstrating hormonal changes associated with follicular maturation and corpus luteum function followed long, anovulatory cycles (Fig. 6).

We have recently reported a luteal phase of 10 days or less in four women who volunteered as normal subjects (16). In two subjects a short luteal phase was found to occur repeatedly in four cycles analyzed over 1 yr. Luteal phase progesterone levels were uniformly low, the mean E_2 peak was significantly below normal, and there was no E_2 rise during the short luteal phase. FSH did not demonstrate the follicular phase increase observed during normal cycles and was significantly less than found in normal cycles during days –9 and –10.

Nine cycles of 24–157 days were studied in seven obese women, three of whom were hirsute (17). All sought medical attention because of irregular menses. In each case menstruation was preceded by hormonal changes associated with follicular maturation and corpus luteum formation. Although in all nine cycles the luteal phase was of more than 10 days duration, P concentrations were uniformly low. The E_2 peak and luteal phase E_2 concentrations were not different from normal. However, as in short luteal phase cycles, FSH during follicular phase days –8 through –11 was significantly less than normal, while LH levels exhibited a normal pattern.

On the basis of these studies we propose a new classification for some clinical patterns of normal and abnormal vaginal bleeding (Table II). It is an initial

TABLE II
A Classification of Menstrual Cycles

Name	Illustrated	Clinical features
Long follicular phase	Figs. 1, 2	Long cycles in young women of normal weight.
Short luteal phase	(16)	Short or normal-length cycles: may be associated with infertility.
Inadequate luteal phase	Fig. 5 (17)	Cycles of variable length found in oligomenorrheic, obese women in the presence or absence of hirsutism and during the menopausal transition.
Short follicular phase	Figs. 3–5	Progressively short, ovulatory cycles with age.
Anovulatory	Fig. 6	Long cycles during menopausal transition.

attempt to describe abnormalities of the menstrual cycle based on disorders of hormonal regulation.

A remarkable feature of the data in the perimenopausal women (Figs. 4–6) indicated that when LH was in the normal range for the cycle stage, FSH levels were consistently elevated in over 400 individual measurements. There are multiple possible interpretations of this finding, including differential regulation of FSH and LH secretion during diminished E_2 concentration at the hypothalamic or pituitary level or differential sensitivity to gonadotropin-releasing hormone.

These data have led us to hypothesize an ovarian regulatory hormone, an inhibin, which would exert a negative feedback control over FSH secretion and which would be reduced in the years before menopause, consequent to a diminished number of follicles. We have not been able to find a previous reference to this possibility.

There are several lines of evidence supporting the presence of an inhibin. First, during menopause, FSH and LH appear to change proportionally when estrogen is given (22–24), and the two appear to rise proportionately after castration (25–26). A similar proportional fall in gonadotropins was noted with the spontaneous rise in E_2 during the two anovulatory cycles of Fig. 6. Therefore, a factor other than the concentration of E_2 must be involved to produce the dissociation of FSH and LH levels seen in the older women. An important recent study has indicated that the presence or absence of ovarian follicles in women with primary or secondary amenorrhea can be predicted accurately by the level of FSH in the serum (27). The absence of follicles resulted in a substantial increase in the FSH concentration regardless of the diagnosis. Although the exceedingly complex events controlling the concentration and changes in concentration of the two gonadotropins during the follicular phase of the normal menstrual cycle have been explained by differential effects of estrogen at the hypothalamus and pituitary (28), the data are also compatible with the presence of another inhibitory regulator of FSH secretion that increases with follicular maturation.

Analogy with data in men provides additional support for the hypothesis. There are no sexually unique hormones, although there are wide variations in the secretion of hormones related to reproduction. Evidence for inhibin in the male is accumulating (29–32), and it has been invoked to account for high levels of FSH and normal levels of LH in oligospermic males (33–35), after testicular irradiation and after cytotoxic chemotherapy (36, 37).

From the viewpoint of physiological need, an inhibin would be an important mechanism for controlling the number of follicles that mature each cycle and would be of special importance in higher species, where the number of conceptuses supportable during a gestation is limited. Finally, the presence of inhibin may aid our interpretation of certain disorders of reproductive function.

From longitudinal studies of the levels of FSH, LH, E_2, and P during normal menstrual cycles throughout reproductive life and in association with certain types of clinical abnormalities, we have suggested a partial classification of menstrual cycle abnormalities (Table II) and have hypothesized the presence of a hormonal control mechanism in women analogous to the inhibin proposed for men.

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