

Perimenopausal Menstrual Problems

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Disturbances of menstrual function in the several years preceding menopause are extremely common. Their pathophysiology most likely relates to the effects of aging on hypothalamic-pituitary-ovarian function and therefore is distinct from menstrual aberrations at other times during a woman's reproductive years. The end result, a lack of regular luteal progesterone secretion, may have important effects on the incidence of neoplasia of the breast and endometrium. Realization of the potential adverse effects of the treatment of menopausal women with unopposed exogenous estrogen may lead to greater utilization of periodic progestin administration during the perimenopausal transition.

Changes of Menstruation With Aging

During the third and fourth decades of life, the interval between menses gradually decreases. Figure 1, taken from an extensive longitudinal study of menstrual intervals throughout life by Treolar et al,¹ shows that the median interval falls from 27.8 days at age 20, to 27.2 days at age 30, and 26.2 days at age 40. Sherman and Korenman² have shown that this lower menstrual interval is due to a shortened follicular phase (Fig. 2).

Beginning 7 years before menopause, the incidence of abnormally short and abnormally long cycles dramatically increases (Fig. 1). During this same time, the mean variability of menstrual intervals in individual women also increases (Fig. 3). It is evident that most women will note this increased variation in the last 5 years before the menopause. The regularity that occurred in 90% of women before age 40 persists to the menopause in only 10% (Fig. 3). Therefore, perimenopausal menstrual disturbance is the rule, rather than the exception.

Endocrine Changes During Perimenopause

Information on hormonal changes during the transition to the menopause is available mainly in the form of cross-sectional studies. The relationship to the longitudinal studies of menstrual function outlined above is mainly by inference. Sherman and Korenman² have compared the levels of circulating gonadotropins and sex steroids in *regularly* menstruating women, aged 40-41 (Fig. 2) and 46-51 (Fig. 4), with those of younger women. These two chronologic periods would approximately correspond respectively to the times immediately before and

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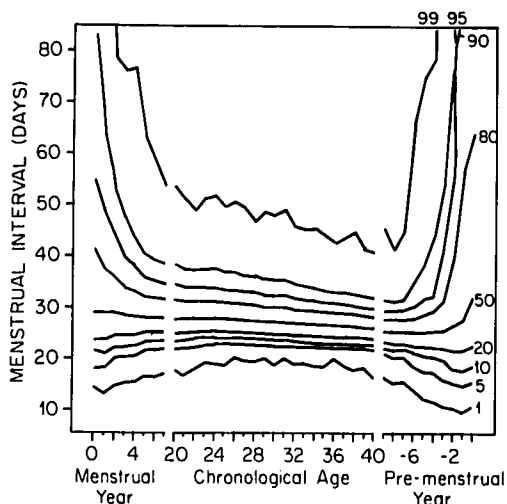
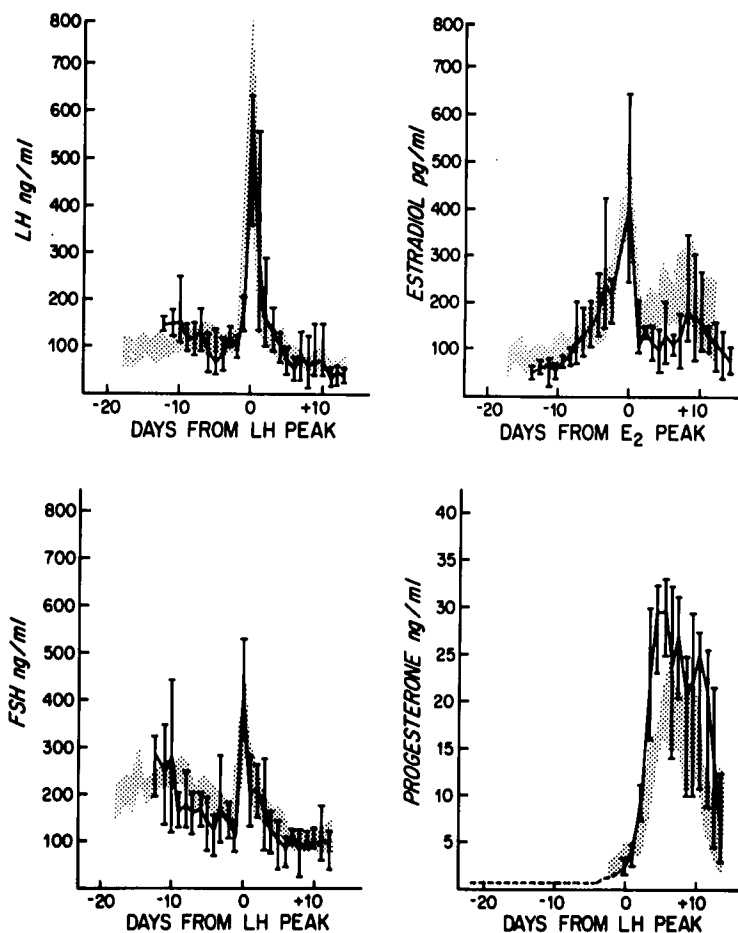


FIG. 1. Contours for the frequency distribution of all menstrual intervals. (Adapted from Treolar et al.¹)

during the time when a marked increase in menstrual irregularity is experienced. In the subjects aged 40-41, the levels of gonadotropins and estradiol were similar to those of the younger women, with the sole difference being a shortened follicular phase. In the women aged 46-51, the concentrations of follicle-stimulating hormone (FSH) were elevated, mainly during the follicular phase. Estradiol levels were lower immediately before ovulation and during the luteal phase than in younger women.

Individual subjects undergoing long-term sampling during periods of irregular menstrual function close to the time of the menopause (Fig. 5) had more pronounced elevations of FSH, often accompanied by elevations of luteinizing hormone (LH).

FIG. 2. The mean and range of serum levels of LH, FSH, estradiol, and progesterone in five women, aged 40-41, compared to the mean \pm SEM in 10 cycles in women, aged 18-30 (shaded portion). (From Sherman et al.² By permission.)



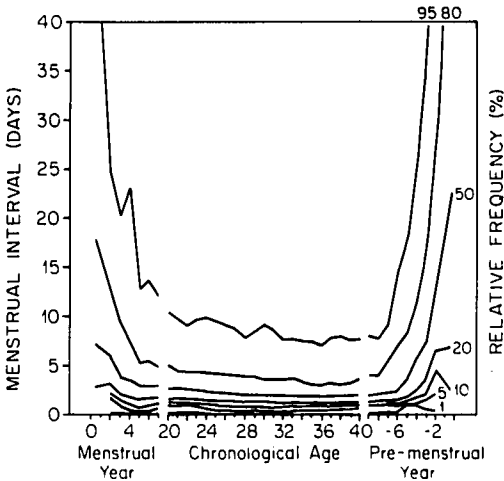


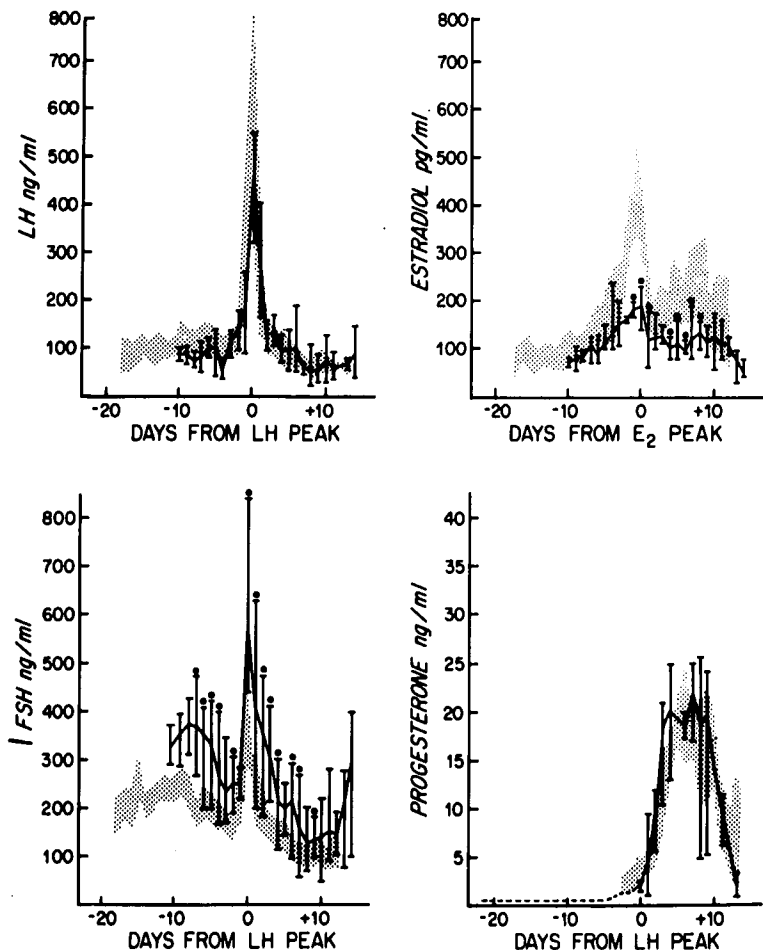
FIG. 3. Contours for the distribution of standard deviations of intervals for all person-years of experience. (Adapted from Treolar *et al.*¹)

Periodic rises of estradiol (Fig. 5) during this time were low in magnitude, compared with the normal preovulatory estrogen surge. Subsequent declines of estradiol were accompanied by anovulatory bleeding episodes (Fig. 5). In another similar investigation,³ five women with an abnormal menstrual pattern who subsequently became menopausal within 1 year had elevations of both FSH and LH.

Pathophysiology of the Perimenopause

The close temporal association of the endocrine changes noted above with the onset of perimenopausal menstrual irregularity suggests a causal relationship. A number of hypotheses have been advanced to attempt to

FIG. 4. The mean and range of serum LH, FSH, estradiol, and progesterone in six women, aged 46–51, with regular menses, compared with the mean \pm SEM in 10 cycles, in women aged 18–30 (shaded portion). An asterisk (*) indicates a statistically significant difference between the values of the two groups, $P < 0.05$. (From Sherman *et al.*² By permission.)



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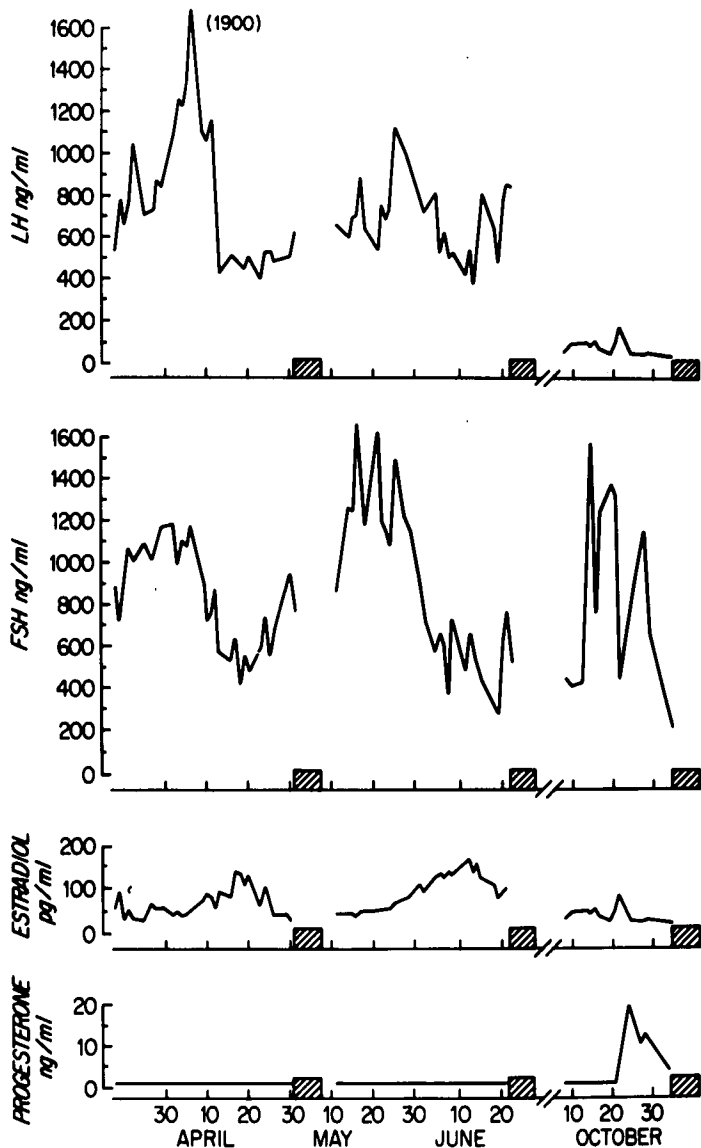


FIG. 5. Daily concentrations of serum LH, FSH, estradiol, and progesterone during three cycles in one 49-year-old subject. Hormone levels are arrayed by calendar date, and the hatched area indicates menstruation. (From Sherman et al.² By permission.)

explain these changes. Sherman and Korenman² have suggested that a declining concentration of ovarian inhibinlike material secondary to depletion of follicles may lead to a selective rise of FSH. Testicular inhibin is most likely a major factor modulating FSH secretion in men. Ovarian inhibin has been demonstrated in subprimate mammals. This theory would not satisfactorily explain the additional sustained rises of LH during the period immediately preceding menopause (Fig. 5). Van Look et al.³ have

suggested that gonadotropin levels may be changed because of altered sensitivity of the hypothalamic-pituitary axis to the feedback effects of estrogen. Others have suggested that the remaining oocytes within the ovary are relatively resistant to gonadotropin stimulation.

In women aged 46–51 with regular menses (Fig. 4), the higher follicular-phase levels of FSH could be explained by either reduced concentrations of ovarian inhibin or a decreased pituitary sensitivity to estrogen feed-

back. However, the follicles being recruited during this later period of regular menstrual function do not appear to be resistant to stimulation. The initial rate of rise of estradiol is similar to that of younger women. The earlier occurrence of the LH surge when estradiol levels are relatively low suggests the possibility of altered hypothalamic-pituitary sensitivity to the positive feedback effect of estrogen.

During the subsequent irregular menstrual function, when both FSH and LH are elevated,^{2,3} high circulating concentrations of gonadotropins are associated with low rises of estradiol. This incomplete follicular maturation in the presence of increased stimulation suggests an element of ovarian resistance. The concept that residual oocytes may be more resistant to gonadotropin stimulation is further supported by the observation of the presence of oocytes after the menopause.⁴ It is possible that the onset of irregularity coincides with the depletion of oocytes with normal responsiveness. The recruitment of the remaining relatively resistant oocytes may be at least in part responsible for the anovulatory function of the perimenopausal ovary.

Diagnosis

In women older than 45, i.e., within the 6-7 years of the mean onset of menopause corresponding to the time when 90% of women manifest increased variability of their menstrual intervals (Fig. 3), abnormal bleeding may reasonably be ascribed to the perimenopausal transition *in the absence of clinical, cytologic, and histologic evidence of another cause*. The importance of this diagnosis is that the occurrence of further episodes of anovulation, "unopposed" estrogen stimulation, and subsequent abnormal bleeding is very likely, whereas earlier in reproductive life these episodes are generally short in duration and self-limited. This difference has important implications in regard to the prophylactic use of cyclic progestins, discussed below. The measurement of FSH may be helpful diagnostically,

particularly in younger women when this cause is suspected.

Neoplasia should be excluded by cytologic study of the endocervix and exocervix and thorough histologic sampling of the endometrium. A recent review⁵ has pointed out that no evidence exists to substantiate the widely held supposition that dilatation and curettage (D and C) is superior to outpatient aspiration for obtaining endometrial tissue. In view of the very high incidence of abnormal bleeding, compared with the relatively low incidence of endometrial cancer in premenopausal women, the conclusion of this author that "D & C probably should not be the primary procedure used for obtaining most samples of endometrium" would appear to be reasonable. This approach, of course, requires sufficient experience with office aspiration to assure an adequate endometrial sample and is untenable in the absence of patient acceptance of potential discomfort of the procedure.

Studies of the characteristics of younger women who develop adenocarcinoma of the endometrium⁶⁻⁸ are helpful in indicating patients at particularly high risk of their abnormal bleeding being caused by a neoplasm. Between 38 and 81 percent of such women are obese^{6,7}; 38-52 percent are nulliparous.^{6,8} Up to 20% have had clinical characteristics of polycystic ovarian disease.⁸ Most of these women (81% in one series) have had a prolonged or even life-long abnormality of menstruation.⁷ In one series,⁶ 6 of 32 patients had coexisting ovarian neoplasms. This association may be due to the increased production of androstenedione in the stroma of the tumor, with subsequent conversion in nonglandular tissues to estrogen⁹ and interference with ovulatory mechanisms. A careful examination of the adnexa is therefore of particular importance in all older women who have abnormal uterine bleeding.

Treatment

During the few years before ovarian function finally ceases, many women are exposed

to significant periods of anovulation and consequent stimulation of the breast and endometrium, uninterrupted by the opposing effects of progesterone. During normal menstrual function, the luteal secretion of progesterone is associated with a decreased concentration of cellular receptors for estrogen and increased conversion of estradiol to estrone by induction of the enzyme 17-hydroxysteroid dehydrogenase. These changes occur both in the endometrium¹⁰ and breast¹¹ and result in reduced estrogen stimulation of these tissues.

The use of estrogen replacement therapy without periodic progestin administration is analogous to periods of anovulation and has been associated with increases in the incidence of cancers of the endometrium¹² and breast.^{13,14} Korenman has proposed that such "estrogen windows" during periods of anovulation are important promoters of carcinogenesis of the breast.¹⁵ The administration of a progestin produces effects on endometrial estrogen receptors and 17-hydroxysteroid dehydrogenase, similar to those occurring during the luteal phase of the menstrual cycle.¹⁶ Cyclic use of progestins has been associated with reductions in the incidence of cancers of the breast¹⁷ and endometrium¹⁸ in postmenopausal women receiving estrogen replacement therapy. Progestin therapy for 10 or more days has been associated with a lower incidence of abnormal endometrial proliferation than courses of a shorter duration.¹⁹ Gambrell has proposed that the periodic administration of a progestin to postmenopausal women who are at increased risk for endometrial cancer should reduce the risk of this tumor.¹⁸ A logical extension of this concept is that cyclic progestin administration in the perimenopause may potentially reduce the subsequent risk of estrogen-dependent neoplasia.

For a woman in the perimenopausal years who develops abnormal uterine bleeding requiring diagnostic evaluation, the use of periodic progestin has two potential benefits. It may prevent future episodes of abnormal bleeding requiring repeated tissue

sampling and in some cases, hysterectomy. It also is accompanied by the theoretic advantage of reducing the woman's cancer risk. If this course is followed, the menopause will be manifested by cessation of withdrawal bleeding, except in those women who have an excess of extraglandular estrogen production. At such a time, the question of replacement of both estrogen and progestin would be logically considered for the treatment of menopausal symptoms and for preventing the sequelae of estrogen deficiency.

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