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Perimenopause: The Complex Endocrinology of the Menopausal Transition

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I. Introduction

MENOPAUSE, and especially the years late after it, are currently understood to carry significant risks for heart disease and osteoporosis (1, 2). These health consequences of the late postmenopause are believed to be caused by low estrogen levels that characterize the hormonal milieu for menopausal women (3–5). In addition to ascribing the late biological consequences of the menopause to low estrogen levels, the emotional and physical symptoms of the menopausal transition are believed to be caused by *decreasing* estrogen levels: "Clearly it is the failing ovarian function and decline in estrogen production that precipitates the menopausal syndrome (including) post-menopausal hot flushes" (6). However, the tendency to focus on menopause as though it were a single event occurring at one point in time (7), and its consequences and symptoms as if they were due primarily to a deficit in estrogen (8, 9), has created both scientific and clinical confusion about the "perimenopause," the period of time that is the transition between the reproductive years and menopause (10).

Another difficulty in the study of the perimenopause is that it has been virtually ignored. The only mention of perimenopause in a recent two-volume gynecological reference text is its definition as "the time preceding the normal menopause during which declining ovarian function causes oligomenorrhea or dysfunctional uterine bleeding, symptoms of estrogen deficiency and elevated gonadotrophins" (11). That definition is in a chapter on premature menopause (11). This same reference publication devotes 160 pages to menopause (11). Likewise, two national consensus documents relating to midlife women do not mention the perimenopause (12) or, only in passing, indicate that perimenopausal women may find oral contraceptive therapy to be useful (13).

The purpose of this review is to integrate the best available data on hormonal levels, menstrual cycles, bone changes, and experiences of perimenopause as a midlife hormonal and sociocultural transition. The primary focus is to review hormonal and spinal bone change data from prospective studies in population-based samples of perimenopausal women. A second purpose is to integrate the available hormonal data into a hypothesis explaining the (patho)physiology of erratic and often high estrogen levels, high [but inconsistent (14)] FSH levels, and prevalent nonovulation in perimenopausal cycles (15, 16). Finally, this review will synthesize the available data to arrive at an understanding of

perimenopause-related symptoms, bone density changes, and to point toward research that is still needed.

Cultural (17, 18) and social status (19) differences in the reporting of midlife symptoms and the meaning of menopause in different societies (20), although very important, have been reviewed elsewhere (9, 21, 22). In addition, because Sowers and La Pietra (2) and Khaw (23) have recently reviewed the epidemiology of menopause, and there are few ways to relate the endocrinological events to the age at menopause, this review will not examine the epidemiology of menopause nor factors contributing to age at onset of menopause (23–27). Finally, this review will not attempt to evaluate the sparse prospective evidence that risk factors for cardiovascular disease increase during the menopausal transition (2, 28, 29).

This review used a systematic search of Medline and Premedline references from 1990 to the present under the following search titles: human, perimenopause, prospective, hormone, vasomotor symptoms (VMS), bone. In addition, earlier epidemiological, histological, and endocrinological sources were used to obtain data on studies on women 45–55 yr of age published before 1990. These sources were supplemented with additional references cited in the papers that were reviewed. All data were assessed for their prospective design and appropriate prospective statistical analysis (*e.g.*, each woman's perimenopausal data compared with her own premenopausal data). Cross-sectional data were excluded unless no comparable prospective data were available.

For the purposes of this review, all sources were critically evaluated for inclusion of sampling methods, physical and sociocultural description of the participants, and methods of assessment of women's experiences, hormone levels, and bone measures. (Because few hormonal studies contained adequate descriptive data on subject selection/exclusion and sociodemographic characteristics, no study was excluded on these grounds).

Primary data on serum hormone levels were all converted into SI units (estradiol was converted from picograms/ml to picomoles/liter through multiplication by 3.671; progesterone was converted from nanograms/ml to nanomoles/liter through multiplication by 3.18). A weighted mean was generated (in which a larger study influenced the mean data proportionately more than a small one). Many data were acquired from graphs or figures; some were in primary tabular form. The variances in SI units were derived from the primary data where possible; ranges are included where no variance could be obtained. A final option was to assume similar variances as those reported in other data sets for the studies lacking them. These data were then combined and analyzed using the Fisher's method of combining *P* values (30). Because hormone assay standards vary, when perimenopausal data were reported, control data from pre- and menopausal women from the same study or, lacking that, from the same laboratory were included for comparison. [For example, the largest population from Melbourne Midlife Women's Health Study (31) did not include any premenopausal control data. Therefore, comparison data were obtained from two studies of premenopausal women from the same laboratory (32, 33).]

Estradiol levels were generally reported for cycle days 4–7 after start of menstrual flow, which is in the early or midfollicular phase (depending on the follicular phase length). This sampling point will be designated simply as the follicular phase (FP) in this review, and the specific cycle days noted if they are different than days 4–7. These days were chosen for hormonal sampling by the Melbourne investigators (31) and those in several other centers and are also in common clinical use. Estradiol and progesterone levels obtained during the week before flow were designated as premenstrual (because ovulation was inconsistent and therefore use of the term "luteal" would often have been inappropriate). For urine hormone levels, it was difficult to compare and combine data from different studies. This is true, in part, because some used overnight data corrected for creatinine (34) and others used 24 h urine collections (35–37) without creatinine correction. Following the suggestion of Metcalf and MacKenzie (38), this review has analyzed the number of days in a cycle in which the total urinary estrogen excretion exceeded the normal midcycle peak (MCP) level in that assay system. The maximum number of days of MCP estrogen levels that should occur is 4 (median, 2; range, 0–4) (38). Using criteria for diagnosis of ovulation in each assay, pregnanediol glucuronide (PDG) levels were interpreted to show whether or not a luteal phase was present; a luteal phase duration of less than 10 days was considered to be a short luteal phase (16).

In the development of an integrating hypothesis for the hormonal changes of the perimenopause, this review sought explanations in the gynecological literature including studies of ovarian hyperstimulation for the purposes of *in vitro* fertilization (IVF) in women over 40 yr of age. The new hypothesis that excessive endogenous ovarian follicular stimulation occurs during the perimenopausal transition (39) is based on the physiology of intra- and extra-ovarian hormonal and paracrine controls of folliculogenesis as described in clinical studies of IVF and investigations in primates, and on cross-sectional anatomical studies of ovarian follicle numbers from ovaries of women of different ages who died or had ovariectomy.

A final aspect of this review is an effort to provide a hormonal or physiological explanation for the changes, symptoms, and signs reported by perimenopausal women. The data support the premise that the perimenopause includes a time of erratic estrogen production (both high and low) and that the times of high estrogen levels (especially coupled with anovulation) are causally associated with significant clinical manifestations such as short or long intermenstrual intervals, heavy flow, increased dysmenorrhea, breast tenderness and nodularity, emotional stress-type experiences, weight gain, and cyclic VMS. It is hoped that a more accurate understanding of the dynamic ovarian hormonal changes of the menopausal transition will lead to needed observational and therapy research and to rational, effective approaches to the education and clinical care of perimenopausal women.

II. Defining the Perimenopause

The World Health Organization (WHO) monograph "Research on the Menopause in the 1990s" formulates the most

appropriate definition of the perimenopause (10). "The term *perimenopause* should include the period immediately before the menopause (when the endocrinological, biological and clinical features of approaching menopause commence) and the first year after menopause (10)." The term *menopausal transition* is used by the WHO to include only the portion of the perimenopause before the final menstrual period. The WHO also urges that the term "climacteric" be "abandoned to avoid confusion" (10) because it is variably used for the entire midlife period, for perimenopause, for the menopausal transition, and as a descriptor for symptoms in the postmenopausal portion of women's lives.

There has been a general consensus for some years that the perimenopause ends when 1 yr has elapsed without menstrual flow (2, 40–43). That is part of the perimenopause definition proposed by the WHO (10). However, menopause is defined by WHO as the "final menstrual period" (retrospectively defined as 1 yr without flow) (10). Therefore, during the last year of the perimenopause, women are also in the "postmenopause" as defined by WHO (10) or are in their first year after menopause (although they cannot know either classification except in retrospect). Because of the 12-month overlap in these definitions, it is difficult to understand whether the year beyond the final menstrual period is or is not included in the perimenopause, even when comparing papers from the same investigators using the same dataset, that focus, respectively, on defining the perimenopause (44), and on describing the normal menopause transition (45). Some reports in the literature even refer to menopause as beginning when 3 or 6 months have elapsed without flow (46), although, in statistical terms, the permanent end of flow requires 12 months without a menstrual period (47). Therefore, although the WHO definition of the perimenopause clearly includes the year after the final menstrual period, the end of the perimenopause and the beginning of menopause are problematic both in definition and in their use in the literature.

The definition of the onset of the perimenopause, like its end, also poses problems for epidemiologists, clinical investigators, physicians, and women. The WHO definition says that it is the period "immediately" (which implies a short span of time) before menopause when the "endocrinological, biological and clinical features of approaching menopause commence" (10). That definition implies that there are a typical set of features that will make onset of the perimenopause obvious. However, variability is the hallmark of the menopausal transition, and no operational definition was given of those features by the WHO (10). A definition of "the inception of perimenopause" for use in epidemiological studies was recently constructed from prospective data of the Massachusetts Women's Health Study (based on a population-based sample of 1,550 women followed for 5 yr) (44). Perimenopause was defined as beginning when the woman reported "at least three but less than 12 months of amenorrhea" or "a self report of increased menstrual irregularity" (44). Those definitions had a positive predictive value of 0.70 for final menstrual period within the next 3 yr (44). For epidemiological purposes, that report and the earlier one (45) found the perimenopause duration to be an average of "about four" years. That is consistent with the 4.8-yr transition documented by Treloar (48) in a prospective study of cycle intervals and symptoms. Women's self-reports of VMS or lighter flow were not very strongly predictive of the onset of perimenopause (44); however, clusters of experiences were not tested as a new factor in the prediction equation. In addition, women who reported a change in cycle regularity "at only isolated interviews" were classified as premenopausal rather than perimenopausal by at least one of the New England Research Institute studies (45), although all participants were over age 45 and 13% of the "premenopausal women" reported VMS (which would be consistent with the "clinical features" of menopause). Finally, about 10% of women apparently changed from pre- to menopausal status between two interviews separated by 9 months (45). [That, of course, is an impossibility if the 12 months of amenorrhea beyond the final menstrual period are considered in the perimenopause as defined by WHO (10).]

It is useful to have an epidemiological definition for the onset of the perimenopause (44). That is especially true because FSH levels increase gradually (49), are often intermittently high and normal, and are not diagnostic (14). If this review's hypothesis about perimenopause physiology is confirmed, it is possible that inhibin levels or inhibin to estradiol relationships might provide a biochemical indicator of the onset of perimenopause. At present, however, a better definition of the onset of the perimenopause is needed for appropriate clinical care as well as for research. It is important for the WHO definition of perimenopause onset to be made into something that can assist a woman to understand what lies ahead for her and that can guide physicians in their care of women in their late thirties through their fifties.

Given the current absence of a biochemical, hormonal, or symptom-cluster marker for the onset of perimenopause, it is possible that women may be able to accurately determine when they begin to be perimenopausal. Dennerstein and colleagues (50) asked women in the Melbourne Women's Midlife Health Study's cross-sectional baseline survey of cycle regularity and flow changes to classify themselves related to whether they believed they had or had not started into the transition, were mid or late in the perimenopause, or had completed it. In ANOVA factor scores, premenstrual complaints were significantly related to dysphoria, vasomotor, skeletal, digestive, respiratory, and general somatic symptoms. These investigators speculate that "self reported menopausal status is a more sensitive measure of endocrine status" (50). However, the subsequent study of hormones in a subset of that Melbourne population did not attempt to use women's self-classification (31), although it found follicular phase estradiol levels that were significantly higher than in premenopausal women reported from the same laboratory (32, 33). Based on the results of this review, an increase in or new onset of high estrogen-related symptoms may signal the onset of perimenopause. If such a symptom cluster were adopted, it is likely that the perimenopause would begin sooner and the transition last longer than an average of 4 yr, as is currently asserted (44, 45).

As outlined above, although extensive work as been done to achieve a consensus about the definition of the perimenopause (9, 10, 44, 45, 50), two difficulties may persist with the current definition: 1) the perimenopause ends at the end of

the year after the final menstrual period, which means it can only be defined in retrospect, and it overlaps with the definition of menopause, and 2) the onset of oligomenorrhea or "irregular flow" may occur after several years of observable changes (that can be hormonally characterized as different from those of premenopausal women). The definition of menopause in retrospect is of little use to the clinician or to the perimenopausal woman prospectively experiencing the transition. A more appropriate definition of the start of menopause is to define it as beginning when a year has passed without flow. The likelihood of a subsequent normal period (*e.g.*, not caused by endometrial hyperplasia, a polyp, or some other pathology) is less than 5% (47). This review includes the last year of no flow in the perimenopause as defined by WHO (10) (and also because hormonal data from many studies to be subsequently reviewed show variable and not consistently low estrogen levels during that time). For the purposes of clarity, this review will term menopause as beginning when a year has elapsed without flow and not as the "final menstrual period" (10).

The WHO definition of the perimenopause does not indicate particular hormonal characteristics. It is commonly understood, however, that this period of time is characterized by declining estrogen levels (6, 11). This review, in contrast, will demonstrate from published data that estrogen levels are highly variable and, in the early part of the perimenopause, estrogen levels average higher than during a woman's reproductive life. Given the lack of clarity about the onset of the perimenopause, all studies were included in this review that characterized women between the ages of 45–55, that used the term "perimenopause," or that indicated that a woman's periods had changed, or that the last menstrual flow occurred within the subsequent 4 yr. In the latter part of this review, an attempt will be made to integrate the clinical and hormonal features of the perimenopause studies into a proposed series of five phases based on clinical and hormonal characteristics.

III. Classic Studies of the Perimenopause

A. Historical studies

Before the current century, menorrhagia was understood to be a dominant characteristic of the perimenopause (51). In 1871, an English physician, Dr. E. J. Tilt, who trained and practiced in France, undertook to systematically describe the transition of 500 of his midlife patients. His remarkable treatise was called *'The Change of Life in Health and Disease: A Practical Treatise on the Nervous and Other Afflictions of Women at the Decline of Life'* (52). Although we do not know over what period he collected these data, or the ages, weights, heights, or sociodemographic characteristics of his patients, this is one of the most dynamic descriptions of the perimenopause yet recorded. His report is valuable because it preceded any effective treatments and allows insight into the perimenopause before the concept of the menopause as a time of estrogen deficiency had become established. Tilt described menorrhagia as occurring on at least one occasion during the transition in 244 of his 500 patients. In addition, he specifically noted that "breast swelling" and "nipple tenderness" were common (52). His pathophysiological explanation for hot flushes and heavy flow were that they provided a necessary release for high "humours." His perspective was "that the change of life is a time of turbulent activity for the reproductive organs. . .they are more (liable) to congestion, hemorrhage, mucous flows and neuralgic afflictions." Tilt clearly viewed what his patients were experiencing as something excessive: flow, mucus, heat generation, breast enlargement (52).

B. Early reports of women's experiences in the perimenopause

Between the time of Tilt's study in the mid-1800s until the 1930s, menorrhagia disappeared from the perimenopause. [Wilbush, an anthropological historian, believes this change occurred because hysterectomy had become prevalent (51).] A new concept that the "complaints" and experiences of midlife women were largely psychological was prevalent in Britain and increased in the early years of this century. The first therapy for menopause in the "modern era" (*e.g.*, when medicine had evolved beyond blood letting and leeches) was apparently the early antiepileptic sedative, phenobarbital. Subsequently, and apparently about the time estrogens were isolated and synthesized in the late 1930s, the idea of menopause changed again. Menopause began to be understood as a time of estrogen deficiency. It was low estrogen levels that explained the psychological symptoms of menopausal women.

By 1953, some "objective" way of characterizing the response of "patients exhibiting endocrine insufficiencies" was needed to monitor responses to estrogenic preparations (53). Blatt, Kupperman, and colleagues developed a systematic description of the timing and quantity of the flow response of a menopausal woman to a given dose and estrogen preparation. The estrogen preparation (and by 1953 there were 17 choices!) was given for 3 weeks followed by a single 100-mg injection of progesterone. The onset, duration, and amount of flow were used to derive an "Amenorrhea index," which predicted the potency of the estrogen (53). A "Menopausal Index" was also created from women's "11 most common menopausal complaints," which has become the standard assessment tool for climacteric experiences (53, 54). The Kupperman and Blatt Index, which divides symptoms into psychological and physical, has been used in most subsequent studies. It included VMS, paresthesia, insomnia, nervousness, melancholia, vertigo, weakness (fatigue), arthralgia and myalgia, headaches, palpitations, and formications. It specifically did not include questions about menstrual flow, breast, weight gain, and fluid symptoms, perhaps because symptoms were *a priori* defined as occurring after menstrual flow had ceased, and because they were understood to be the consequence of estrogen deficiency.

Neugarten and Kraines (55), behavioral scientists with the Committee on Human Development in Chicago, used the previously developed Kupperman and Blatt Menopausal Index (53, 54), combined with symptoms reported by patients and their physicians to occur in midlife, to derive a 22-item menopausal symptom instrument which they published in 1964. Their new instrument included weight gain, flooding,

irregular cycles, cold hands, trouble concentrating, and breast pain as well as feelings of suffocation. This new instrument was reproducible to retest within women ($r = 0.8$) and correlated well with the Kupperman and Blatt Menopause Index ($r = 0.7$).

The Neugarten Menopause Symptoms instrument was validated through its completion by women of different ages. The responses of a large sample of adolescent girls, midreproductive life women, women over 40 reporting some change in cycles (who were perimenopausal but whom the authors called "menopausal"), and women more than a year after their last menstrual flow were all compared (55). Perimenopausal women shared with adolescents (and not with normally menstruating women or those after menopause) the experiences of weight gain, cold hands and feet, feeling excitable and blue, and having headaches. Significantly more than any other group of women, the perimenopausal women experienced "weight gain, cold hands and feet, skin crawls, headaches, feeling blue, cold sweats, tired feelings, excitable, can't concentrate, crying spells." The group of women who were more than 1 yr beyond their last flow were the least symptomatic of any of the groups (55). Neugarten and Kraines' interpretion of their data stated: "the increased production of sex hormones in adolescence (signaled by the first menses) and the decreased production of estrogen (signaled by menopause) . . . are primary in producing heightened sensitivity to and the increased frequency of reported symptoms" (55). That the menopausal women 1 yr after their last period were the least symptomatic was ascribed to an improved ability to cope (55).

C. Early prospective menstrual cycle interval and basal temperature documentation

The first physiological, longitudinal study of the perimenopausal transition was an anecdotal study of two women, reported in 1949 by a physiologist, Mary Collett (56). This study documented the transition into the menopause by yearly cycle interval averages and ranges in one woman (recorded from 34–48 yr of age), and primary cycle interval data from a second subject (from 41–57 yr of age). Basal metabolic rate (BMR) was periodically documented in subject 1. The BMR showed a marked decrease of 14.5–18%, which occurred at the age of 45, coincident with the onset of her cycle interval irregularity. The rate continued to be suppressed until age 48, when she had her last menstrual flow. During her mid-forties she experienced an initial weight gain of 14 kg (56). This was followed by "Evidences of endocrine imbalance . . . weight loss along with falling BMR, softening of the teeth at 46 to 48, low hemoglobin. . . , hot flushes, great fatigue and extreme nervousness." The other subject's prospective data showed marked menstrual cycle variability (from 19–89 days in length) beginning 4 yr before the last flow (56). This initial study is still one of the few that has followed women prospectively from the premenopause through to the menopause.

Several large descriptive, prospective studies were begun in the late 1940s, at a time before hormonal measurements from urine or blood were widely available. Women were asked to record the day on which flow began on calendar cards, or calendars were coupled with basal temperature records (as a bioassay for progesterone action). These studies have documented menstrual cycle characteristics in women of different ages both cross-sectionally and prospectively (16, 47, 48, 57, 58). Collett performed one of the earliest published studies in which an unknown number of women recorded 302 cycles (57). The longest continuous sample was 176 cycles in a woman in her forties. Collett noted that with increasing age, cycle intervals shortened (from a mean of 30 days in the youngest to a mean of 25 in the oldest), that the follicular phase also shortened, and that anovulation increased to 15% of the cycles in the oldest women (57).

Two large prospective cycle interval studies, by Chiazze *et al.* (59) and Treloar *et al.* (47), showed shortening cycle intervals from a mean of 29 days for women in their twenties to a mean of 26 days for women in their forties. Treloar and colleagues prospectively followed more than 2,700 women over an average of 5 yr. A number of women recorded from their twenties until they were menopausal (47, 48). Although initially the sample only included women who were undergraduates at the University of Minnesota, it later included some of their daughters and friends. Annual questionnaires documented surgeries, pregnancies, and hormone use, which, along with age and postsecondary education, have been used in data analysis (47, 48).

The volunteers for Treloar *et al*. recorded the onset of flow on a menstrual card. No data about ovulation were available. The 120 women providing data through menopause (47) showed "heterogeneity," with an increase in both short and long cycle intervals (which was noted to be similar to that after puberty) (47). In a subsequent questionnaire, 14% of women reported hot flushes in the years preceding the cessation of flow (48). The cycle interval changes noted for women in their late forties and early fifties are similar to those documented by Doring [n = 67 (58)], by Collett *et al.* [n = 43 (57)], and by Vollman [n = 41 (16)], who sampled women from infertility clinics, from general advertising, or from a general medical practice, respectively.

The largest prospective basal temperature study was by a Swiss physician named Vollman (16). More than 1 yr of prospective, quantitatively analyzed rectal basal temperature data were documented in 332 women, and the perimenopausal transition was prospectively recorded in 41 women (16). [It is of interest that Vollman developed the first quantitative method for evaluation of luteal phase onset from basal temperature data—the day the temperature curve crosses the mean temperature line correlates with the day of the midcycle LH peak day ($r = 0.891$, $P < 0.001$)(60).] As shown in Fig. 1, which depicts the last 100 cycles of one woman (16), 9% of the cycles were less than 21 days in length, and 10% were greater than 36 days long. In contrast to Vollman's documented 4% mean rate of nonovulation for women in their mid-twenties to early forties, 16% of this woman's perimenopausal cycles were nonovulatory (16). Stratifying the data by gynecological age (years from menarche), Vollman noted that 34% of cycles were anovulatory in women of gynecological age 40–45. In addition, Vollman (16) observed that, even within cycles that were ovulatory, an increasing percentage of cycles of older women had short luteal phase lengths of less than 10 days.

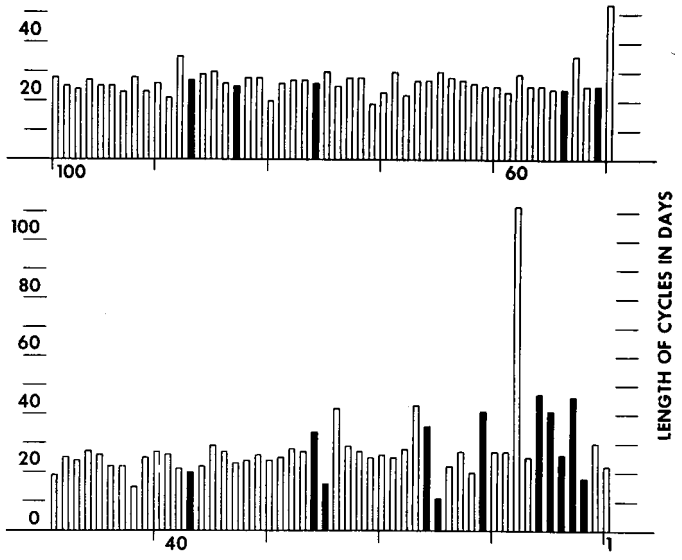

FIG. 1. This bar graph shows a continuous menstrual cycle data set during the perimenopausal transition in one Swiss woman. These are the final 100 cycles graphed to show cycle interval as an *open bar* (if the cycle was ovulatory based on quantitative mean temperature analysis of rectal basal temperature) and *solid bar* if the cycle was anovulatory. [Reprinted with permission of the publisher from Vollman RF, Friedman EA (eds) *Major Problems in Obstetrics and Gynecology*. W. B. Saunders, Co., Toronto, 1977, Fig. 50, p.105) (16).].

These studies have thus documented that the first changes of menstrual cycles during the perimenopause are shortening of cycle intervals (which has subsequently shown to relate to shortening of follicular phase lengths) (16, 57). Ovulation also becomes unpredictable and then rare during the perimenopause (58, 61–65). The 50% perimenopausal prevalence of anovulation by longitudinal basal temperature data is similar to that documented in later hormonal studies (15, 66). However, at present, prospective data derived from population-based samples concerning cycle-by-cycle changes in interval, flow, and ovulatory characteristics are still lacking. Ideally, information about menstrual cycle and related characteristics needs to be monitored through the entire midlife transition from the late premenopausal years until at least a year has passed since the final menstrual period.

IV. Prospective Epidemiological Studies of the Perimenopause

Population-based data that are prospectively collected can potentially differentiate the perimenopausal period from the earlier premenopausal state and from the subsequent menopausal state. However, no project to date has integrated women's menstrual cycle characteristics or cycle-by-cycle hormonal changes with their health assessments, "symptoms," use of medical services, or long-term morbidity. Despite this, and the lack of hormonal data in these studies, a brief look at the prospective epidemiology of the perimenopausal period is useful. The following two North American studies used similar questionnaires and analytic strategies, were both based on telephone interviews every 6 to 9 months, and, along with studies conducted in Japan by Dr. Margaret Lock of Montreal, have been used to frame some important cross-cultural understanding of menopause (9, 20, 21).

A. Manitoba Project on Women and Their Health in the Middle Years

The Manitoba Project, which began in the early 1980s, has provided a wealth of information about the perimenopausal period of women's lives (7, 21, 40, 41, 67–77). Although the original sample was not strictly population based, the design and subsequent conduct of the study met the best of epidemiological principles. The design included interview of women over the telephone at 6-monthly intervals for 3 yr. The initial cohort of 477 women, ages 45–55, represented 87% of the sample of an earlier cross-sectional study (40). An analysis of the longitudinal reports of menstrual periods documented that more than 100 different patterns of menstrual flow (*e.g.*, regular followed by a skipped period, or no flow for 3 months followed by every other month) occurred in just over 300 women (40). Menstrual flooding, in addition to "menstrual problems, lack of energy, and nervous tension," were the best predictors of a change from regular to irregular cycles (40). In a subsequent analysis, depression scores over 16 on the Centre for Epidemiological Studies Depression Scale occurred in 26% of all of the women at one time or another in the 3 yr of the study. In a cross-sectional analysis of the prospective data, neither change in menstrual cycle status nor children leaving home were associated with depression, but having a hysterectomy was (76). However, the potential for a causal relationship between the endocrine changes that led to flooding and the mood symptoms appears not to have been adequately considered in the Manitoba (76) study (or in the Massachusetts study described below) (42).

B. Massachusetts Women's Health Study

This important study, which was initiated in 1981, observed 2,570 women, aged 45–55, who were identified using census lists. This study achieved a 77% initial response rate, and 93% of those participated during the entire 4.5-yr prospective study (61), which has provided key information about midlife women (21, 26, 42, 44, 45, 78–82). Women were contacted by telephone every 9 months and were asked standardized questions concerning their menstrual cycle status as well as other experiences (similar to the questions and instruments used in the Manitoba Project). Those who had menstruated in the preceding 3 months and reported no change, or only intermittent changes in cycle regularity, on one of two consecutive interviews were called premenopausal; those with irregularity or 3–11 months of no flow were called perimenopausal; and those who were more than 12 months beyond their last flow were classified as menopausal. By these criteria, 1,178 of the sample were premenopausal at the initial telephone interview (45). Excluding women with surgical menopause, the average age of onset of the perimenopause was 47.5 yr, and menopause occurred at an average age of 51.3 yr (26, 45). The average duration from onset of irregular periods until 12 months past the last flow was approximately 4 yr. Nulliparous women and smokers

started the perimenopause at a slightly younger age (45). Smokers and those starting perimeopause at a later age experienced a shorter perimenopausal transition. Smokers were approximately 2 yr younger at menopause (45).

Perimenopausal women tended to be more symptomatic (VMS, musculoskeletal symptoms, anxiety, fatigue, sleep disturbances, gastrointestinal concerns) than women menstruating regularly and those a year beyond their last flow. Approximately 20% of perimenopausal women visited their physician early in the transition with concerns about their menstrual cycles, while 12% sought help late in the transition because of symptoms they defined as menopausal (45, 61). It appeared that women with a longer perimenopausal transition were more likely to report VMS. Very few of the perimenopausal women were treated with ovarian hormone therapy or oral contraceptive agents (45, 82).

C. Kuopio Osteoporosis Risk Factor and Prevention (OSTPRE) Study

Tuppurainen and colleagues (46) reported on the design of the OSTPRE study in which all 14,220 women ages 47–56 in Kuopio Province were surveyed by a postal enquiry sent in 1989. This is the largest population-based study of the menopausal transition to date but includes no published hormonal nor menstrual cycle data. There was a 92.8% response rate to the questionnaire, which included anthropomorphic and gynecological topics, use of medication, disease diagnosis, and fractures. In addition to the lack of hormonal data, the study has several drawbacks: menopause is defined as beginning after 6 months without flow; no category is provided for the perimenopause (although the mean age of all women was 52); and 21.7% of women aged 56 were still menstruating, probably because of hormone therapy. As evidence of its careful epidemiological design, however, the Kuopio study undertook a reproducibility analysis (repeat questionnaire completion by a sample) that showed moderate correlations for milk and cheese consumption ($r = 0.548$ and 0.469), high correlations for weight, height, and oral contraceptive use ($r = 0.81$ to 0.93), and low correlations for physical activity in hours per day ($r = 0.212$, $P = 0.03$) (46). In addition, they proved the validity of their questionnaire for fractures against computerized medical records and showed only three false-positive and three false-negative reports out of a total of 2,935 fractures.

The epidemiological data from Kupio include age at hysterectomy. A total of 7,826 gynecological operations were performed on the 13,100 women who were followed longitudinally; 0.9% of these operations were because of cancer. Hysterectomy was performed in 15.8% of the population [which is lower than is reported from studies in the United States and Canada (67) but greater than in Japan]. The peak incidence of hysterectomy is 13.5/1,000 person years between the ages of 46–48 yr. The incidence was at or above 10/1000 person years from ages 40 to 52, which effectively spans the ages in which the perimenopause occurs in a North American population. These data are of importance because high estradiol levels and disturbed ovulation, which this review documents to occur during the perimenopause, are likely to be causal in abnormal menstrual bleeding problems (83), which are a common reason for hysterectomy.

The average age for the 13,100 women at the start of prospective observation in the Kuopio study was 52.4 yr; they had a body mass index (BMI) of 26.3 and consumed 817.2 mg/day of calcium from dairy products. Twelve percent of the population smoked regularly, and 8.7% had never been pregnant. At baseline, menopausal symptoms were reported by 55% of the "premenopausal" women (*i.e.*, women who had experienced flow in the last 6 months) and by 69% of the postmenopausal women (who were 6 months or more beyond their last menstrual period). The bone and fracture data from this study will be reported in *Section IX.C.* (46).

The above three prospective studies of the epidemiology of the perimenopause have provided important information about women's symptoms, the timing of events, and the process of the perimenopause. However, none of these studies has included detailed (more frequent than every 6- to 9-month telephone questionnaire) self-reports of experiences, primary menstrual cycle information, or hormone levels. To provide the needed direct hormonal information about the perimenopause, detailed physiological studies (the majority of which lack population-based validity) must be reviewed.

V. Systematic Studies of the Endocrinology of the Perimenopause

A. Cross-sectional (single-cycle) hormonal studies in the perimenopause

The results of 12 studies (of which 9 used serum monitoring and 3 employed urine assessments) are shown in Table 1. The designs of the hormonal studies in perimenopausal women performed to date, except for the population-based Melbourne Women's Midlife Health Study (31) and the Malmo, Sweden, study (84), have reported data from selected groups of women (often gynecology patients or hospital staff paid for their participation) and have not described the subjects adequately for comparison with other studies. The Melbourne population-based study appropriately reported the response rate (56%) and women's descriptive characteristics (31) but separated the hormonal data (31) and symptom information (50) except for one paper cross-sectionally comparing follicular phase hormone levels in women with and without VMS (85). Also, no primary menstrual cycle data are available, although the hormonal analysis is in five different groups based on reported menstrual cycle characteristics (*i.e.*, Group I includes women who reported no change in cycle interval or flow in the last year, and Group V designates women reporting no period for 3 months but who had experienced flow within the last 12 months). Despite this menstrual cycle classification (whose validity has been questioned) (86), the Melbourne Women's Midlife Health Study, as now reported, does not allow integration of data on hormonal levels with perimenopausal flow characteristics, vasomotor, and other experiences of perimenopausal women.

The usual design of these cross-sectional studies was hormonal sampling (by urine or serum) at weekly intervals

TABLE 1. Cross-sectional hormonal studies of the perimenopause

Reference	Author (yr)	n	Age	Subject selection	Design	Estradiol (pmol/liter ± SD)	Progesterone (nmol/liter ± SD)	% Ovulatory	Comments E_2 in controls
					Serum data				
92	England *et al.* (1974)	3	ND	ND	Daily × 24 days	'Cycle' mean 238	ND	ND	30 controls EF 97.7 ± 20 PreM 213 ± 20
89	Reyes *et al.* (1977)	12	48–50	ND	Every 5–7 days × 4	FP 180 ± 147 PreM 239 ± 147	15.8 ± ?	100[a]	15 controls EF 73 ± 51 PreM 330 ± 165
90	Abe *et al.* (1983)	5	43–45	Hospital staff (paid)	Every 3–4 days	FP 78 ± ? (50–200)	ND	38	9 controls EF 66 ± 20 PreM ND
65	Ballinger *et al.* (1987)	25	40–55	Gynecology and workers	Every 7 days × 4	FP 300 ± 100 (SE) PreM 450 ± 150 (SE)	16.25 ± ?	ND[a]	29 controls EF 280 ± 80 (SE) Luteal progesterone PreM 340 ± 180 (SE) 26.2 nmol/liter
196	Cutler *et al.* (1987)	52	39–55	Newspaper ads	One sample	EEF 245 (55–459)	ND	ND	No controls
91	Lee *et al.* (1988)	16	46–50	Gynecology and workers	Daily × 1 cycle	FP 175 ± 60 PreM 560 (370–850)	ND	ND	41 controls EF 167 ± 60 PreM 400 (300–550)
31	Burger *et al.* (1995)	277	45–57	Random population	One sample	FP 226 (50–1900)	ND	ND	No controls < 45 yr
99	Reame *et al.* (1996)	16	40–50	Staff, students, ads	3 per cycle	FP 175 ± 24 (SE) PreM 156 ± 34 (SE)	2.8 ± 0.8 (SE)	ND	16 controls EF 122 ± 17 (SE) PreM 179 ± 30 (SE)
100	Klein *et al.* (1996)	9	40–50	Selected	FP daily	FP 267 (205–400) PreM ND	ND	ND	13 controls EF 199 pmol/liter (190–207)

Summary data for serum estradiol

FP serum estradiol
Perimenopause (n = 415), 225 ± 98 pmol/liter
Controls (n = 292), 175 ± 57 pmol/liter
Fisher's F = 16.12; $P = 0.041$

Premenstrual serum estradiol
Perimenopause (n = 69), 371 ± 97 pmol/liter
Controls (n = 250), 303 ± 84 pmol/liter
Fisher's F = 15.46; $P = 0.0164$

						E	PDG		Cycle
					Urinary data				
87	Papanicolau *et al.* (1969)	3	42–51	Gynecological clinic[b]	24 h urines 48 h pool	MCP × 8 days 1/4 cycles	Low in 3/4	50	1 Short nonovulatory MCP for 10 days
88	Adamopoulos *et al.* (1971)	3	40–49	Gynecological clinic[b]	24 h urines 48 h pool	2 Cycles with >MCP 12, 14 days	Low in all	0	1 Short cycle, nonovulatory E ↑ during flow
63	Van Look *et al.* (1997)	6	37–51	Gynecological clinic[b]	24 h urines every 3 days	5/6 abnormal ↑ E 6, 15, 5, 5, days >MCP	Normal in one	34	E ↑ during flow Short follicular phases Heavy flow, short cycles

ND, No data; FP, early follicular phase (days 4–7 of cycle unless specified); PreM, the week before onset of flow (or luteal phase in ovulatory cycles); EEF, cycle days 1–5; MCP, midcycle peak estrogen level; E_2, estradiol; ↑, increased; E, estrogen excretion; PDG, pregnanediol glucuronide excretion.

[a] Excluded non-ovulatory cycles or women.

[b] Dysfunctional uterine bleeding.

across one cycle (63, 65, 87–91). However, other studies have employed different designs: one study measured levels once in the follicular phase (31), and another measured levels daily over approximately 24 days in three perimenopausal women (92). The nine studies providing serum data are listed first in Table 1, and the three with urine measurements are listed subsequently. All are in chronological order by date of publication. FSH and LH changes through the perimenopause, although documented in many of the cited studies, will not be reviewed here. These data confirm what has been known for many years, that with increasing gynecological age, FSH levels increase first followed by LH levels (32, 91, 93, 94), and that an elevated FSH level is not diagnostic of perimenopause (14). These data also confirm that the early follicular phase is the time in the cycle during which FSH is most likely to first be elevated (91).

In contrast to the expectation that perimenopausal estradiol levels are on the decline or are low, many studies have shown at least one cycle or group of subjects in whom follicular phase estrogen levels were high (31, 87–91, 95). This anecdotal observation of erratic high estradiol levels, however, has been confirmed by mean data and by this meta-analysis. Mean FP estradiol levels taken from 415 perimenopausal women were compared with mean FP levels in 292 premenopausal controls reported in 12 different papers (32, 33, 65, 89–93, 96–100). As shown in Table 1, the mean FP estradiol level in perimenopausal women was higher than in controls (224.9 ± 98 *vs.* 174.7 ± 57 pmol/liter). A Fisher's combined *P* test of the four studies that provided serum samples of both pre- and perimenopausal women (65, 89, 91, 99) showed significantly higher estradiol levels in the FP in perimenopausal women (Fisher's F = 16.13, df = 2 k = 2 x 4 = 8; $P = 0.041$).

The most convincing evidence that FP estradiol levels are inappropriately high during the perimenopause comes from the Melbourne Women's Midlife Health Study, which provides the largest number of women cross-sectionally sampled in a well designed population-based study. FP estradiol data, by cycle and flow-based categories, are illustrated in (Fig. 2) (31). Average estradiol levels *did* significantly decrease across the five menstrual cycle groups with a lower level in the group who reported skipping three or more cycles. Group I, who reported no change in cycle interval or flow in the preceding year and were considered premenopausal, had a FP estradiol geometric mean of 273 pmol/liter, while that mean was 113 pmol/liter in Group V (31). However, excluding data from Group I (who may have been either pre- or perimenopausal) still leaves a weighted *mean* estradiol level of 226 pmol/liter, which is high compared with mean EF phase estradiol of 173 pmol/liter in normal young women controls in two studies published by the same laboratory (184 ± 30 and 162 ± 73 pmol/liter, respectively)

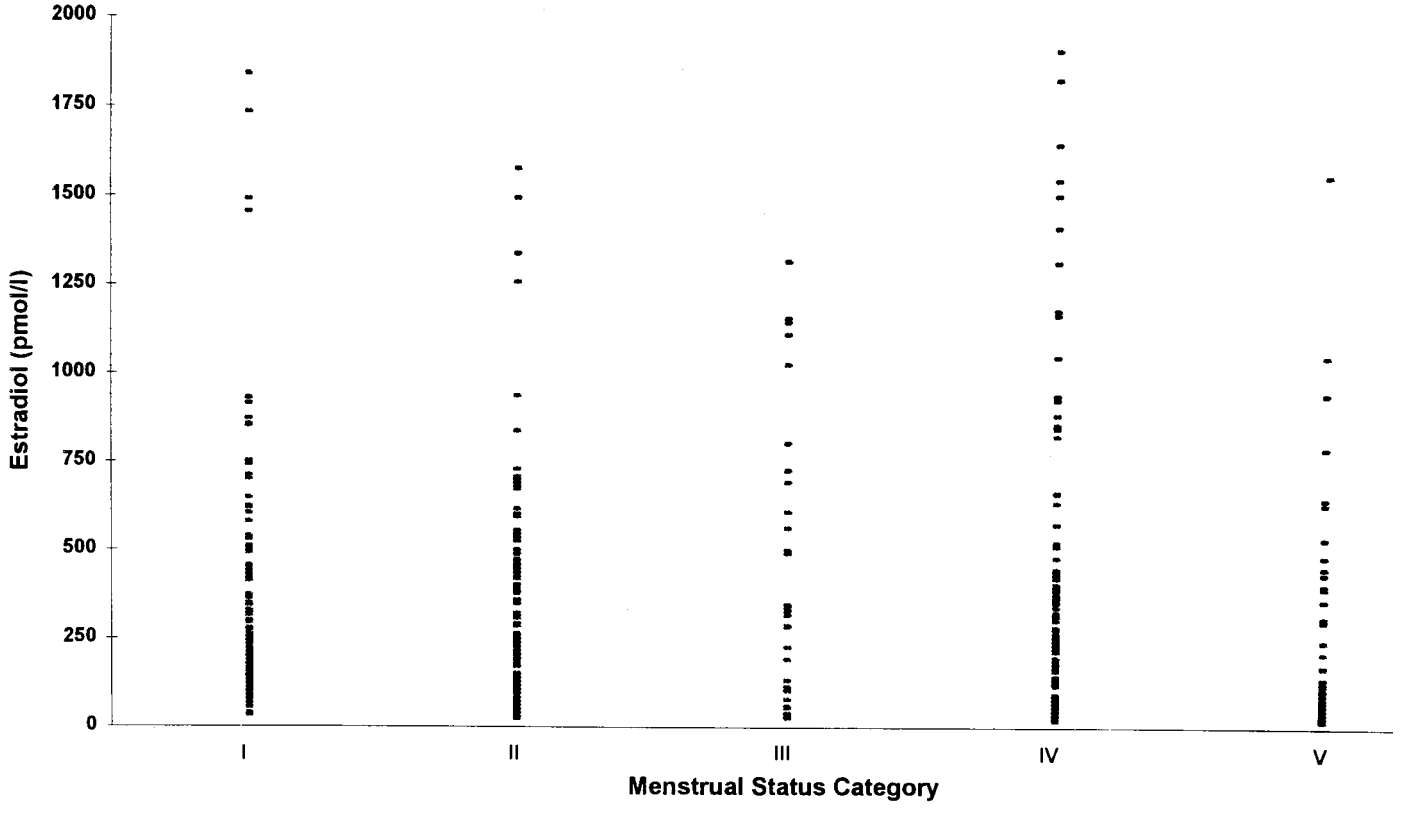

FIG. 2. This scatter plot shows the range and values of FP serum estradiol levels (in picomoles/liter) obtained days 4–7 of the menstrual cycle in Groups I through IV and at random in Group V (the 50 women who had been without flow for ≥ 3 but <12 months). Group I includes 103 menstruating women over 45 yr old who had experienced no menstrual changes in the preceding year; Group II includes 89 women with changes in flow; Group III describes 33 women with changes in cycle frequency; and Group IV includes 105 women who experienced changes in both flow and frequency. Note that normal midcycle estradiol peak levels are about 750 pmol/liter. [Reprinted with permission from H. G. Burger *et al.*: *J Clin Endocrinol Metab* 80:3537–3545, 1995 (31). © The Endocrine Society.]

(32, 33). The average estradiol levels are higher than normal premenopausal FP phase levels for all except the last group (86). In addition to the higher mean estradiol levels, more than 10% of the individual values in every group exceeded the mean laboratory normal midcycle estradiol peak level of 750 pmol/liter (32, 33) (Fig. 2).

The mean FP estradiol level of 225 pmol/liter from combined data in 415 perimenopausal women as shown in Table 1 is more striking because in young women FP estradiol levels are low and range from 50–200 pmol/liter, with a mean of 175 ± 57 pmol/liter in the combined premenopausal controls (Table 1). The high perimenopausal FP levels published by Burger and colleagues (31) are, in fact, not different from cycle mean estradiol levels (obtained by quantitative combined FP and midluteal phase samples) from two cycles in each of 66 ovulatory women studied in this laboratory (86, 101).

Estradiol levels during the premenstrual (or luteal phase) portion of the cycle are also significantly elevated in perimenopausal women (Table 1). The mean premenstrual estradiol level exceeded the mean in premenopausal controls (371 ± 97 *vs.* 304 ± 84 pmol/liter). Although only a subset of studies provided systematically studied data from both pre- and perimenopausal women (65, 89, 99), Fisher's combined *P* test shows perimenopausal levels to be significantly elevated ($F = 15.55$, $df = 2k = 2 \times 3 = 6$; $P = 0.0164$) compared with normal premenopausal values.

The three cross-sectional studies in which urinary hormonal data were used also showed elevated estrogen levels, this time as estrogen excretions. Before lending too much weight to these data, it is worth remembering that all of these studies sampled women with abnormal flow and ovulatory disturbances (63, 87, 88). Seven of the 12 cycles showed individual cycle estrogen excretions to be high (greater than MCP levels) for durations of 8, 12, 14, 6, 15, 5, and 5 days, respectively (63, 87, 88). In addition, dysfunctional uterine bleeding was observed to be associated with high estrogen excretions that occurred during flow (87). Thus, whether by urine or serum testing, one of the characteristics of the perimenopause is high mean estrogen excretions or estradiol levels, both in the FP and premenstrually. These data, however, do not indicate that every perimenopausal woman experiences high estradiol levels consistently, nor can we yet understand what percentage of women and for what periods of time will be exposed to high estrogen levels.

Studies of ovulatory characteristics or progesterone levels are few in perimenopausal women in contrast to the many studies that have documented estradiol levels or estrogen excretions. Of the 12 studies of perimenopausal endocrinology shown in Table 1, all of those measuring urine excretions but only two of those measuring serum hormones tabulated the percentage of the cycles that were ovulatory. In paid midwifery students studied by Abe *et al.* (90), five of eight cycles were nonovulatory. Two studies excluded otherwise eligible women because they were nonovulatory (89, 100). Despite excluding 24% of the sample, the midluteal progesterone levels averaged 15.75 nmol/liter in women ages 45–50 compared with 39.65 nmol/liter in women ages 20–29 ($P < 0.05$) (89). That suggests ovulatory but insufficient luteal phase cycles were occurring. Although Ballinger *et al*. (65) do not categorize cycles as nonovulatory or ovulatory, they showed significantly lower mean progesterone values (16.3 *vs.* 25.3 nmol/liter) in women in the later perimenopause compared with controls. Furthermore, Ballinger *et al*. showed that mean progesterone levels over 16 nmol/liter (*e.g.*, indicating ovulation) occurred on only one rather than two of the weekly samples in women ≥45 yr old compared with those less than 45 (65). These data suggest ovulatory but short luteal phase cycles, as previously shown by Vollman (16), occur more frequently in the menopausal transition. Studies by Lee *et al.* (91) and Fitzgerald and co-workers (98) did not document any age-related differences in progesterone levels. Unfortunately, The Melbourne Midlife Women's Health Study provides no information about ovulation (31).

The three cross-sectional studies in which 24-h urinary PDG levels were reported (Table 1), as previously mentioned, all sampled women with abnormal bleeding or from gynecological patient populations (63, 87, 88). In these three studies, anovulation occurred 77% of the time. This appears to exceed the frequency of anovulation from other studies of the perimenopause (15, 16). This lends support to a probable causal relationship between dysfunctional uterine bleeding and lower levels of progesterone (83). Therefore, these cross-sectional data confirm the earlier basal temperature studies (16, 57, 58) showing a significantly increased frequency of cycles having ovulation disturbances (anovulation, short or insufficient luteal phases) during the menopausal transition.

In summary, these cross-sectional data describing the serum hormonal characteristics of one cycle each from 415 perimenopausal women show that mean estradiol levels, both in the follicular and premenstrual phases, are significantly higher than in younger women. Although this observation may be caused by sampling relatively later in a shortened FP, or in some cycles in which midcycle bleeding rather than normal menstruation was occurring (86), approximately 10% of levels are extremely high and exceed the normal MCP estradiol level (Fig. 2) (31). Also, when cycles are aligned by their MCPs as is done by Santoro and colleagues (34), FP values remain higher in perimenopausal than in premenopausal women. In addition to higher FP estradiol values, premenstrual estradiol levels are also higher than in premenopausal controls. In general, these papers do not comment on the high estrogen levels they document. This omission may occur because high estrogen levels were contrary to their anticipated results (86). Finally, perimenopausal women have a higher (by almost 50%) frequency of anovulation compared with women in their twenties and thirties (16). Despite the many studies and data from large numbers of women that strengthen these conclusions, prospective data are needed to confirm them and to understand the physiological changes leading to higher estrogen productions and disturbed ovulation that appear to characterize the perimenopause.

B. Prospective ovarian hormonal levels in the perimenopause

Eight studies, spanning the years from 1976 to 1996, have recorded hormone levels over several menstrual cycles in each of a total of 248 women. These data are reported in detail

in Table 2. Although some studies report only summary data, 193 cycles are shown in detail in the respective publications (34, 38, 61, 84, 93, 102–104). These data differ from the single-cycle cross-sectional data in that they allow some appreciation of the cycle-by-cycle hormonal variability of the perimenopause. All except three of the prospective hormonal data sets have been obtained from 24-h or overnight urine samples rather than serum measurements because it is less invasive. As shown in Table 2, high and prolonged or inappropriately timed (such as the start of flow) and high estrogen levels (as high as the MCP) are documented in several studies (34, 38, 87, 102). Although it is counterintuitive, both Longcope *et al*. (103) and Metcalf and MacKenzie (38) documented high estrogen levels during long cycles, or, in one instance, in a perimenopausal woman who subsequently did not have further vaginal bleeding.

The strongest data with which to understand the endocrinology of the perimenopause are those that prospectively cover the time from premenopausal cycles through to menopause. Although describing only two women, Brown (102) has reported cycle data for the last 6 or 7 yr of the transition. Menstrual flow and vaginal mucus were reported daily, and 24 h urines were collected weekly by each of these two women (102). (The "Billings" or "symptothermal" method of natural family planning uses the woman's self-report of the stretchiness of the vaginal mucus as a rather accurate "bioassay" for estrogen effect) (105, 106). The data show remarkable variations in estrogen excretions within each woman and over time. Using as a reference the normal mean cycle urinary estrogen for young women of 26.1 ± 2.15 μg/24 h (102), the mean urinary estrogen levels were 44.1 and 30.8 μg/24 h, respectively, taken from weekly samples over the entire 6 or 7 yr, including a final year without flow. These estrogen levels are *not* low but are 69 and 18%, respectively, higher than premenopausal mean levels (102).

Based on urinary PDG excretion in the prospective perimenopausal data from two women, only 56% of the 38 cycles were ovulatory. The patterns of urinary estrogen, mucus, and bleeding show anovulatory cycles with high premenstrual estrogen levels followed by cycles with short FP that are normally ovulatory. Typically, that ovulatory cycle might be followed by a very long FP cycle with a short luteal phase length. In a few instances, the well-trained subjects did not record stretchy mucus despite high estrogen and low PDG excretions. That observation suggests some decrease in cervical gland responsiveness to estrogen may develop during the perimenopause (102).

Three prospective studies reported in Table 2 used serum sampling (84, 93, 103). Only the Sherman study (93) sampled daily across several cycles in three women while the others measured serum levels at 3- to 6-month intervals in 39 and 152 women, respectively (84, 103). Sherman and colleagues summarized their data to say that FSH levels were rising and estradiol levels were declining in women ages 46–56 with regular cycles. However, when the hormonal data are examined more closely, they include several characteristics suggesting intermittent high estrogen levels. For example, in 4 of 13 cycles shown in detail, estradiol levels over 260 pmol/liter occurred at the time of flow, a time when levels have normally dropped. In addition, 3 of 13 cycles showed clearly

TABLE 2. Prospective hormonal studies of the perimenopause

Reference	First Author (yr)	No. of women[a] (cycles)	Age	Subject selection	Design	Duration (cycles/sub)	Estrogen (pmol/liter ± SD)	% Ovulatory	Comments
93	Sherman (1976)	8 (13)	46–55	Hospital staff (paid)	Daily serum E_2, P, FSH	(3–6)	E_2 > 260 on day 1 in 4 cycles	7 nl 43 SLP	Cycle lengths 1–62 days 3 short follicular phases 2 cycles with heavy flow
61	Metcalf (1979)	31 (127)	>40	Housewives Hospital staff	Weekly urine E, PDG	(3)	22% of cycles had E > MCP for > 14 days/cycle	52	Normally only 2 days > MCP/cycle
38	Metcalf (1985)	30	>40	Housewives Hospital staff	Weekly urine E, PDG	(3)		52	
102	Brown (1985)	85 (2 women, 38)	ND	Natural family planning	Weekly urine	6–7 yr	Total E means 44.1 and 30.8 μg/24 hr, respectively	56	Normal total E per cycle = 26.1 ± 2.15 μg/24 hr
103	Longcope (1986)	39 (ND)	45–58	ND	Serum every 3–4 months	2.5 yr	Weighted mean E_2 294 ± 327 (180–790)	ND	No control data
104	Shideler (1989)	5 (10)	42–47	Gynecology patients (paid)	Daily urine E, PDG	(3–4)	4/10 MCP at day 1, 15 days > MCP in 50-day cycle	40 nl 40 SLP	Cycle lengths 22–70 + days
84	Rannevik (1995)	152 (ND)	47.8–48.5	Population based	Serum E_2 every 3–6 months	12 yr	Weighted mean E_2 378.8 (64–640)	ND	60% ovulatory 7 yr and 4.8% 6–0 months before last flow
34	Santoro (1996)	11 (5)	>47	Newspaper ads	Daily AM urine	(4)	10-day >MCP, E_1 76.9 ng/mg Cr	60	Controls E_1 40.7 ng/mg Cr; no flow on graph

ND, no data; FP, follicular phase; PDG, pregnanediol glucuronide; MCP, midcycle peak levels; nl, ovulatory with luteal phase length ≥10 days; E, urinary total estrogen excretion; E_2, estradiol; P, progesterone; SLP, short luteal phase; Cr, creatinine.

[a] Number is the number of women (no. of cycles shown in detail).

short FP lengths (93). Normative data for menstrual cycle hormone levels show a significant inverse relationship between the FP length and the mean FP estradiol level ($r = -0.551$) (96). Therefore, the data of Sherman *et al*. (93), although not documenting high mean estradiol levels, show intermittent high values. Also, two of the three women whose cycles were shown in detail had at least one anovulatory cycle. Longcope's study, which sampled 39 perimenopausal women at 3- or 4-month intervals for 2.5 yr, found that the weighted mean estradiol level was 294 ± 327 pmol/liter, which is clearly not low (103) compared with a mean cycle estradiol level of 275 ± 112 pmol/liter in 66 ovulatory premenopausal women (101).

The Malmo Perimenopause Project, which includes 152 women who contributed serum hormone samples every 6 months during the interval from 80 months before up to more than 48 months after the last flow (84), has recently published the largest and best designed set of prospective data. Unfortunately, as in the Longcope study (103), serum samples were not timed within cycles. Data are presented according to how many months the women were before or beyond their final menstrual period. This presentation indicates that the mean estradiol level was 379 pmol/liter during the perimenopause (as defined by the 48 months before and the 12 months after the last flow). The mean serum estradiol level, however, was 459 pmol/liter if only the 4 yr *before* the last flow were included (84). Even in the year after the last flow, during which the mean estradiol levels were 182 ± 163 and 171 ± 151 pmol/liter (for the first and the final 6 months, respectively), these estradiol levels were normal for the premenopausal FP (Table 1).

The Malmo study also shows a high estradiol variance (as SD of 427 for a mean of 513 pmol/liter) when women were 4 yr before the last flow (84). This variance may be due to the collection of serum with no relationship to flow or may be a vivid expression of the variability as well as the elevation of estradiol levels during the perimenopausal transition. In both the Malmo and the Massachusetts study by Longcope, the estradiol variance did not become less than 50% of the mean until approximately 24–48 months had passed since the last flow (84, 103). Thus, the three prospective studies of the perimenopause in which serum hormonal sampling was used, like the cross-sectional data, show high estradiol levels.

The first of several prospective studies in which urinary hormone measurements were used focused on the incidence of ovulation disturbances during three consecutive cycles in women 40 to 55 yr old (61). Metcalf documented that anovulation occurred in more than 50% of women reporting a recent history of oligomenorrhea (who were classified as perimenopausal). Anovulation, however, was present in only 5% of cycles in those who reported regular cycles, even if they were more than 50 yr old (61). Ovulation was inconsistent in 66% of women who noted recent changes in cycle length. In two other reports from New Zealand with similar design, 17 of 31 perimenopausal women ovulated within 16 weeks of their final menstrual period (15) or 52% of perimenopausal women were ovulatory (66). Midcycle spotting occurred for 12 of 139 women; 5 of these had regular and consistently ovulatory cycles, and 4 of the 7 with irregular cycles also had inconsistent ovulation (61).

The prospective urinary hormone studies from New Zealand described above included no estrogen data (15, 61, 66). However, some years later the urinary estrogen excretion data from the same set of subjects were reported indirectly as a ratio of estrogen excretion divided by PDG excretion (107). In 22% of the cycles, the ratio of estrogen to PDG excretion at or above 100 (which is typical of the midcycle estrogen peak) lasted for a prolonged time of 14 or more days. In their 16 normal premenopausal women, the urinary midcycle ratio of hormones over 100 averaged 2 days and had a range of 0–5 days (107). Extremely high ratios (>100) occurred on only 18% of cycle days in younger women while ratios over 100 were present on 40% of the measurement days in the perimenopausal women ($P < 0.01$) (107). Furthermore, as mentioned above, the longer the cycle the more likely it was that a prolonged high ratio would occur. Ratios over 100 for ≥ 14 days occurred in 6.9% of cycles that were 18–35 days in length, and in 46.9% of cycles that were 50–260 days long (107). Although low PDG levels, as expected in long anovulatory cycles might be postulated to explain this, a ratio over 100 required high estrogen excretion (which was *not* anticipated in oligomenorrhea).

The two further prospective studies using urinary steroid excretion levels corrected for creatinine were authored by Shideler and colleagues (104) and by Santoro and colleagues (34). These two studies show from three to six cycles of daily urinary data in detail for each of several women (Table 2). Furthermore, Santoro's group systematically compared urinary hormonal data from 11 regularly cycling women over 47 yr old (whom she called perimenopausal) with data from younger women also studied across one cycle. These data, which are illustrated in Fig. 3, show significantly increased estrogen excretions in both the follicular and premenstrual phases of the cycle in the older women (34). The mean estrone level of 76.9 ng/mg Cr is clearly greater than the mean level of 40.7 ng/mg Cr in controls (34). The final important observation from these data is that PDG excretion was significantly less in regularly cycling women over 47 yr old compared with younger women ($P < 0.015$) (34) (Fig. 3). These data confirm lower progesterone excretion levels during the early perimenopause and suggest, in contrast to the Metcalf data, that short or insufficient luteal phases may begin before anovulation develops and that these subtle ovulation disturbances are present before menstrual cycles become irregular or oligomenorrhea develops. Data from the groups of Shidelar and Santoro show that high estrone conjugate excretion (at greater than midcycle levels) exists for prolonged periods that last from 3–13 days (34, 104) as illustrated in Fig. 4. Unfortunately, Santoro *et al*. do not record times of vaginal bleeding on this graph or allow a calculation of the FP lengths which Shideler *et al*. noted to be short during several cycles (104).

In summary, these prospective studies over extended periods of time in a total of 248 perimenopausal women indicate that estrogen levels (or excretions) are, at least intermittently, quite high. Likewise, ovulatory disturbances are more prevalent in the perimenopausal period than they have been since the years immediately after menarche. The cycles with high estrogen levels are also often anovulatory, which may contribute to the heavy bleeding reported by many peri-

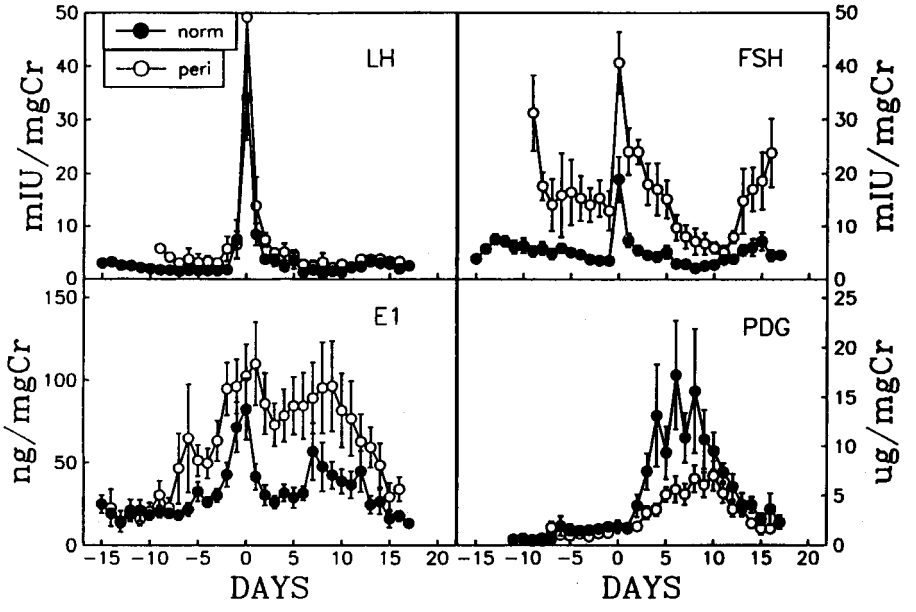

FIG. 3. This composite graph shows the mean ± SEM of daily urinary LH, FSH, estrone conjugates (E_1), and PDG excretions corrected for creatinine and standardized to the day of presumed ovulation (day 0) in 11 regularly menstruating perimenopausal women (*open circles*) compared with 11 younger women (*closed circles*). E_1 was higher in the perimenopausal women ($P = 0.023$), and integrated PDG was lower ($P = 0.015$). [Reprinted with permission of N. Santoro *et al.*: *J Clin Endocrinol Metab* 81:1495–1501, 1996 (34). © The Endocrine Society.]

menopausal women (40). Although Santoro makes the assertion that women experiencing premature ovarian failure differ from women experiencing perimenopause at a normal age, it is of importance that the women with premature ovarian failure she studied were selected to have been "amenorrheic for at least 6 months," while the perimenopausal women were selected to have regular periods and "no period of amenorrhea exceeding 3 months in the past year" (34). Therefore, it is likely that those women with premature menopause were in a later stage of the menopausal transition than were the perimenopausal women reported by Santoro and colleagues. Based on these data, it is not clear that the perimenopausal transition differs for women experiencing it abnormally early.

Both the cross-sectional (Table 1) and prospective (Table 2) published studies on the endocrinology of the perimenopause just reviewed show consistent evidence of significantly higher estrogen levels than are normal in younger women. This observation contrasts sharply with our current understanding. Is it possible that, until recently, estrogen levels did gradually decrease during the perimenopausal transition? That is highly unlikely given that the time of acquisition of these data spans more than 20 yr, and that evidence of high estrogen levels such as menorrhagia and breast tenderness have been reported to occur during the perimenopausal transition since Tilt's time, and short FPs since the 1950s (57). The endocrinology of the perimenopause has not recently changed. Rather, the construct that menopause is a time of low estrogen production likely led to an inability of scientists and clinicians to see the (intermittently) high estrogen levels that were present (86).

VI. Histological Studies of Ovarian Changes Across the Lifespan

To understand the origin of the ovulation disturbances and high estrogen levels documented in the perimenopause, the ovaries themselves may provide information. Hormone production by the ovaries of women who are beyond menopause has previously been reviewed (103, 108–110). Rather than reiterate that work, this section will review recent work on the structure and histology of human ovaries in women of different ages to reevaluate the changes that relate to the perimenopause.

It is well established that, from birth onward, primordial follicles are continuously being activated, maturing partially, and then regressing. This follicle activation continues in a constant pattern that is independent of pituitary stimulation. Evidence suggests that this regular follicular activation changes during late reproductive life. Richardson and colleagues (111) performed a careful quantitative histological study of the ovaries and endometrium coupled with a single hormonal measurement and a reproductive history on a randomly selected ovary from each of 17 women ages 44 to 55 who underwent ovariectomy and hysterectomy for uterine fibroids or menorrhagia. (Although these are important data, the women were a selected and abnormal sample because they apparently required hysterectomy.) The six women reporting regular cycles had an average of 1700 follicles in the ovary compared with an average of 180 follicles in the ovaries of those who reported irregular cycles (111). The endometria from the perimenopausal women showed no evidence of ovulation although three of seven, by timing, should have been in the luteal phase. Furthermore, in contrast with this review's reported endocrinology of the perimenopause (Tables 1 and 2), estrogen levels were equal in the premenopausal and perimenopausal women and ranged from 146 to over 450 pmol/liter, which is well within normal ranges for the menstrual cycle (96).

The steady number of follicles undergoing partial stimulation and atresia without any hormonal intervention does not appear to increase at puberty (112), although few peripubertal ovaries have been examined thus far. The marked increase in pituitary stimulation of the ovary at puberty does not appear to alter that follicular "depletion rate" (112, 113). A number of pathologists have performed quantitative anal-

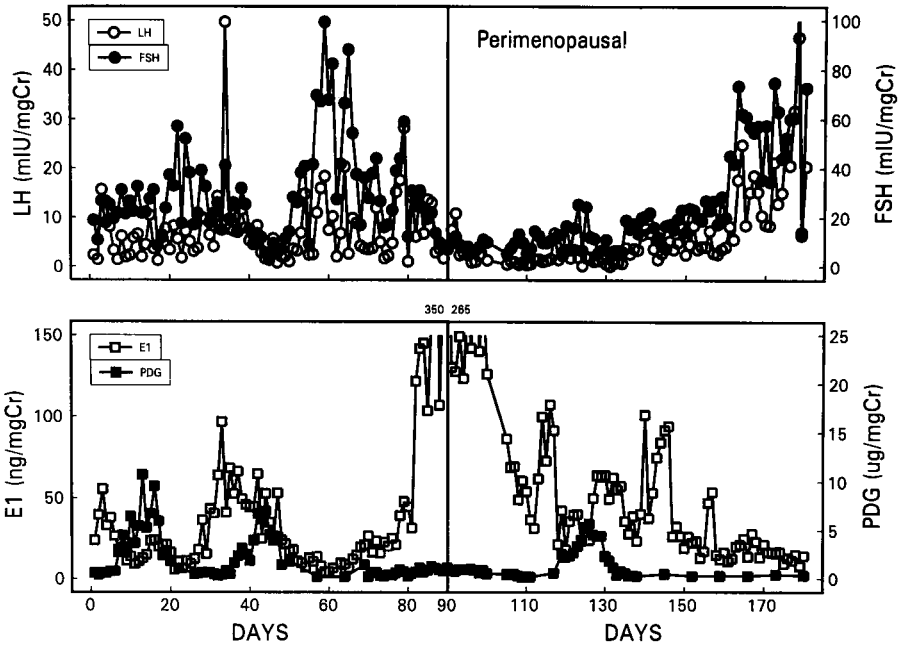

FIG. 4. This composite graph shows the mean ± SEM of daily urinary LH, FSH, estrone conjugates (E_1), and PDG excretions corrected for creatinine over a continuous 160-day period of time in one perimenopausal woman. Note the prolonged high E_1 levels associated with anovulation between days 80 and 110. [Reprinted with permission from N. Santoro *et al.*: *J Clin Endocrinol Metab* 81:1495–1501, 1996 (34). © The Endocrine Society.]

ysis of the remaining ovarian follicles in ovaries of women from random autopsy series or women having ovarian surgery (111–114). Only recently, however, has the remaining number of follicles been related to the age of the woman to construct an age-specific rate of apparent follicle disappearance (113). When the cross-sectional ovarian follicle count data are ordered by the age of the woman examined, observations show a marked increase in the slope of follicle loss that appears to indicate an accelerated rate of follicle depletion beginning in the late thirties or early forties (111–114).

What are the implications of an accelerated rate of follicle depletion? It seems obvious that more follicles would disappear if more were being stimulated consequent to gonadotrophin levels that begin to rise in women in their thirties (49). Another possibility is that the cohort of follicles, although normal in number, develops more rapidly. That would explain the shortened FPs but does not account for the accelerated rate of follicle depletion that has been observed. Is it likely that these morphological observations are associated with changes in hormonal production in the perimenopause? To date, this question cannot be answered. Clearly, a larger number of ovaries from a nonselected series of women is needed to systematically study follicle numbers and hormonal levels in women dying suddenly during both the peripubertal years and during the late thirties through to the sixties.

The ovary in perimenopausal and menopausal women is an active endocrine organ that has not yet been adequately studied. The time of increasing depletion of follicle numbers appears to correspond with a time when the ovaries are under increasing stimulation from rising FSH levels. Could the estrogen production of a larger cohort of partially stimulated follicles (few of which ovulate) explain the preserved or high estrogen productions documented during the perimenopause? Could the increased rate of dizygotic twinning that increases with increased maternal age also provide evidence for the stimulation of multiple follicles in the perimenopause?

VII. Physiological Studies of Changing Ovarian Hormones in Women in Their Forties and Fifties

This section proposes to examine the recent literature relating to ovarian folliculogenesis and atresia in older women. In addition, it must include a review of the data, much of it new, concerning the changing production and actions of inhibin across the life of a woman. These concepts may aid in understanding the physiology of hormonal changes occurring during the perimenopause.

The last two decades have seen a rapid increase in studies of exogenous ovarian hyperstimulation for ovulation induction in infertility treatment and the investigation of the control of folliculogenesis and fertility. This is especially true as increasing numbers of women who have delayed their first pregnancy until their late thirties and early forties are found to be relatively infertile. In parallel with studies of IVF and embryo transfer in women over 40, is an increasing appreciation of the roles of inhibin, not only in feedback inhibition of FSH secretion in women, but also as a possible indicator of ovarian reserve (115–117), and as a paracrine factor in ovarian physiology (118). The following sections will review this physiological literature with an eye to illuminating the hormonal changes during the perimenopausal period.

A. Folliculogenesis and ovarian hyperstimulation for in vitro fertilization (IVF)

Just as it has been known for many years that FSH levels increase with increasing gynecological age in normal women (32, 91, 93, 94), so has it been evident that an elevated early FP FSH level carries a negative prognosis for pregnancy during IVF (119, 120). In a systematic study of pregnancy

rates during IVF in 29 women above age 40 compared with women in younger age groups, the older women had as many oocytes recovered at laparoscopy, equal estrogen and progesterone levels, but more oocytes with fractured zonae. The pregnancy rate was also equal (~30% with multiple preembryos transferred) to that in younger women, but 60% of the older women (compared with 30%) subsequently spontaneously aborted (119). Inhibin responses to exogenous hyperstimulation were significantly lower in women older than 35, although estradiol responses were not related to age (117). Luteal phase inhibin levels correlated significantly with progesterone levels ($r = 0.87$). Finally, it is possible that the inhibin response to maximal ovarian stimulation might predict the onset of perimenopause (117), although this needs to be systematically tested in well matched, regularly cycling women whose ages range from 30–50.

The variability of the early FP FSH in women of greater gynecological age is probably important to the perimenopause. Not only is FSH known to increase during the early FP in women in their late thirties and early forties, the elevated FSH is variable from cycle to cycle (14, 120). The reproductive medicine unit in London, Ontario, Canada, investigated whether a single raised FSH (>20 IU/liter) on day 3, followed by a normal one in the cycle in which IVF was undertaken, carried an adverse pregnancy prognosis. In a cohort examination of 1,868 IVF cycles, women who currently had a normal day 3 FSH level, but for whom it had been elevated once in the past, had a pregnancy rate reduced to 5.6% compared with 16.5% in those with consistently normal FSH levels. No pregnancies occurred if two previous FSH levels had been raised, even though the FSH level was normal in the cycle in which IVF was used. Thus, when the FP FSH is *ever* raised, some aspect of ovarian folliculogenesis appears to have changed.

To investigate hormonal changes occurring in women over 45 who continued to report regular menstrual cycles, MacNaughton and colleagues (32) studied nine such women compared with nine women from each of the age groups: twenties, thirties, and early forties. Volunteers were selected among regularly cycling clinic employees who were not receiving exogenous hormones. A FP serum sample (days 4–7) and a midluteal phase serum sample were analyzed for FSH, LH, estradiol, progesterone, and inhibin (32). Using ANOVA, women 45 yr old or over had lower FP inhibin levels as well as higher FSH levels but no consistent difference in estradiol levels. Again, inhibin was lower in the luteal phase in the older women (as will be discussed below), but FSH, LH, progesterone, and estradiol were not different (32). FSH levels during the early FP were negatively correlated with estradiol ($r = -0.35$, $P < 0.05$) suggesting some element of normal feedback inhibition; no correlations existed during the luteal phase (32). In a study of similar design, 11 women ages 37 to 45 reporting regular cycles were recruited from hospital staff and contrasted with similar women ages 21–25 (n = 14), 26–31 (n = 13), and 32–36 (n = 15) who met the same criteria (98). In addition to measurements of estradiol and progesterone, serial pelvic ultrasound scanning was performed for both follicular cyst number and size and for endometrial thickness monitoring (98). In this study, the FP was longer (16 days) in women over 37 (which contrasts with the short FPs shown in older women in large longitudinal basal temperature studies (16, 57) and in the perimenopausal endocrinology reviewed above). The maximum follicle diameter was 17 mm and significantly smaller than in younger women ($P < 0.01$). MCP estradiol levels were equal in all age groups as were maximal luteal phase progesterone levels, but there was a tendency for the day 8 estradiol to be elevated in the older age group (range 115–352 compared with 111–268 pmol/liter) and a mean of 234 *vs.* 171 pmol/liter ($P = 0.17$). It is of interest and probable clinical importance that the endometrial thickness at its maximal during the luteal phase was significantly greater in women over 37 compared with both groups of younger women (Fig. 5) (98).

Early FP elevations of estradiol, although increasingly seen to be a characteristic of cycles in women over 40 (31, 34, 98, 102), like elevated FSH levels, have been shown to be negatively related to pregnancy rate in IVF (121, 122). Two studies have concluded that day 3 estradiol levels over 275 or 367 pmol/liter, respectively, were associated with no pregnancy in 27 or 30 studied women, and that this observation was true whether or not FSH levels were normal (121, 122). One third of the cycles having a day 3 estradiol level over 367 pmol/liter had to be cancelled to prevent ovarian hyperstimulation syndrome. This contrasted with a cancellation rate of only 0.4% in those with estradiol levels of less than 294 pmol/liter (122). This was true although the same number of ampules of hMG were used and the same peak estradiol levels were achieved in all cycles (122). Therefore, some increased responsiveness in the follicular pool appears to occur when the early FP estradiol level is raised. The elevated EP estradiol levels just described (121, 122) were remarkably similar to those in women from the Melbourne Women's Midlife Health Study (31) (Fig. 2).

B. Inhibin physiology in women over 40

Thus far, many puzzling hormonal characteristics of menstrual cycles in midlife women remain to be explained. These puzzling aspects include observations that: 1) elevated early FP FSH levels occur despite normal or high estradiol levels (which should be suppressing FSH); 2) an increased risk for

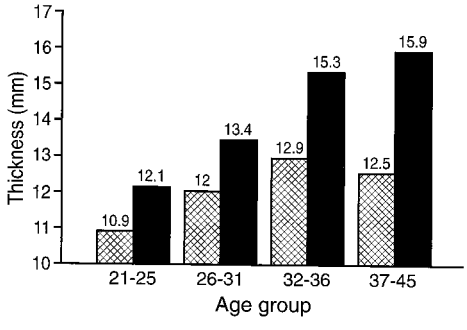

FIG. 5. This bar graph shows the endometrial thickness (in millimeters) by pelvic ultrasound on the day of presumed ovulation (*open bars*) and at maximal thickness during the luteal phase (*solid bars*) in women of different ages as shown on the x axis. The endometrial thickness premenstrually was greatest in the older age group (15.9 mm *vs.* 12.1 mm in the youngest women, $P < 0.001$). [Reprinted with permission of the publisher from C. T. Fitzgerald *et al.*: *Br J Obstet Gynaecol* 101:229–233, 1994 (98)].

ovarian hyperstimulation and multiple stimulated follicles exists during IVF in cycles having elevated early FP FSH or estradiol levels; 3) an increased endometrial thickness occurs in older women despite similar estradiol and progesterone levels as younger women; and 4) an apparently depleted pool of potential follicles and low fertility rates after age 40 coexist with maintained estradiol levels (which must be produced by ovarian follicles). All of these different characteristics of cycles in women in their forties point toward some change in the regulation of folliculogenesis in older regularly menstruating women. Is it possible that ovarian inhibin production plays a role in this process and can explain some of these observations?

As reviewed above, mean estradiol levels are normal or high in perimenopausal women, and FSH levels are often not suppressed despite these high estradiol levels. These aspects of pituitary-ovarian relationships are contrary to expected physiology. It is proposed that decreasing ovarian production of inhibin plays a role in the high average estrogen levels documented during the perimenopause. More specifically, the B subtype of inhibin, a small peptide made in ovarian granulosa cells, which is known to be stimulated by FSH and, in turn, to suppress FSH, may play a role in the altered physiology of the perimenopause (100, 123). Increasing evidence suggests that ovarian inhibin plays a role in ovarian folliculogenesis (115, 117); therefore, new information about inhibin levels and their functional relationships in women in their forties and fifties becomes important.

Inhibin is a small pleomorphic peptide made within the ovarian granulosa and luteinized granulosa cells, which, although assay specificity and sensitivity are still problematic, has been shown to be important in ovarian physiology (123). Inhibin may be an intraovarian regulator [although other peptides such as activin and follistatin are more likely paracrine factors (118)] but one of its more important functions appears to be feedback suppression of FSH production (116). Inhibin is produced by the granulosa cells of the corpus luteum and, in a lesser amount, by granulosa cells of the growing follicle during the FP. FSH stimulates inhibin (124), which in turn suppresses FSH.

Women with what is called "incipient ovarian failure," based on higher early FP FSH levels, have been shown to have lower FP inhibin levels than controls (125). These women, who experienced an ovulatory cycle after therapy with estrogen and cyclic progesterone, had normal estradiol levels. Their vaginal ultrasounds indicated multiple small follicular cysts and inappropriate follicular maturation (125). In both the follicular and luteal phases, inhibin and FSH levels within the same cycles were inversely related. In response to follicular stimulation with clomiphene and hMG, women over 35 had lower levels of inhibin, although estradiol levels were equivalent to those in women in their twenties and early thirties (117). In addition, luteinized granulosa cells harvested from women with low and high day 3 FSH levels showed, respectively, high and low inhibin secretions *in vitro* (116). Women with high FSH levels, although producing normal amounts of estradiol and progesterone, have lower levels of total inhibin and dimeric inhibin (116).

The most recent and important evidence suggesting that inhibin is instrumental in the menstrual cycle changes of women in their forties (and probably in the perimenopause) was obtained from a cross-sectional study of the FP in ovulatory women of ages 40–45 (n = 10) compared with women of ages 20–25 (n = 13) (100). The protocol involved observation until a 16-mm cyst was visible on ultrasound or until estradiol levels exceeded 550 pmol/liter, at which time 10,000 IU of hCG was administered. This study, which sampled serum daily from onset of menstruation and obtained vaginal ultrasounds daily in the early FP, documented that inhibin B levels were lower while both FSH and estradiol levels were higher in the older women (Fig. 6) (100). The authors speculated that inhibin B is a product of primary and early antral follicles while inhibin A is produced by the dominant follicle. Although the biochemistry and measurement of inhibin and its forms remain to be fully clarified, the dynamic association of low inhibin B levels with high FSH and high estradiol in the early FP is the best evidence of the role of inhibin in the physiological changes occurring in the menstrual cycles of women in their forties. Do these observations relate to the endocrinology of the perimenopause?

VIII. Hypotheses to Explain Perimenopausal Endocrinology

A. Pathophysiology of the proposed perimenopausal endogenous ovarian hyperstimulation syndrome

A hypothesis is needed that will explain the confusing endocrinology of the perimenopause (39). The hypothesis presented here proposes that the perimenopausal increases in estrogen levels are produced from an increase in the number of follicles in a stimulated cohort responding to rising FSH levels. Lower levels of inhibin production in the luteal and follicular phases could explain the rising FSH levels in the early FP (14, 100, 126). As shown diagramatically in Fig. 7, in contrast to the ovaries during the premenopausal early FP, the decreased inhibin production during the perimenopause allows a small but important rise in FSH. This increased FSH causes more follicles to be recruited [thus leading to the observed increased rate of follicular depletion (111, 113)] as these follicles, usually without progressing to ovulation, eventually involute. As would be expected, each of these recruited follicles makes a finite amount of estradiol. Together, these multiple recruited follicles produce the elevated FP estradiol levels previously documented in the perimenopause (Tables 1 and 2) and in IVF studies (121, 122). That more follicles are recruited is also suggested by the multiple small follicular cysts noted in older women during IVF (119) and observed after suppression with ovarian hormone therapy (125). That more follicles are stimulated is also supported by the increased tendency for dizygotic twinning in older mothers (127).

Further support for the hypothesis that small increases in FSH level can lead to "ovarian hyperstimulation" is found in a recent case study in which there was a pathological reason for disturbed pituitary-ovarian feedback: a 37-yr-old woman with an autonomous FSH-secreting pituitary adenoma presented with irregular cycles, heavy flow, and multiple ovarian cysts. Her previously resected tumor was documented to have regrown (128). This woman's FSH levels were in the

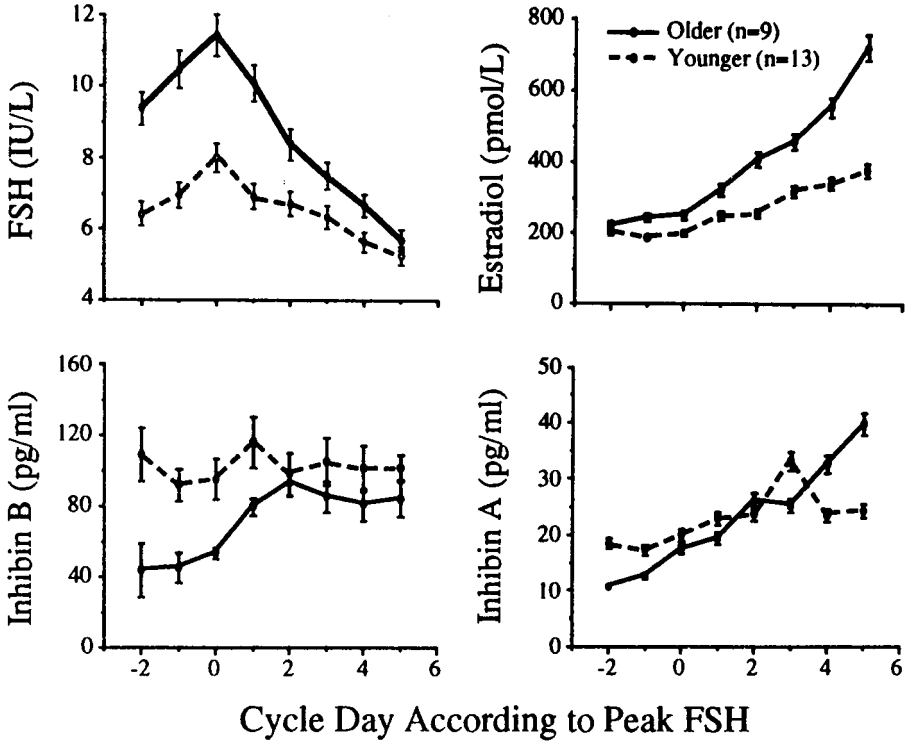

FIG. 6. This composite graph shows the mean ± SEM concentrations of serum FSH, E_2 (estradiol), inhibin B, and inhibin A presented in relationship to the day of the peak level of FSH (day 0) in two groups of women: nine women ages 40–45 (*solid line*, "older"), and 13 women ages 20–25 (*dashed line*, "younger"). E_2 levels were significantly higher ($P = 0.002$) and inhibin B levels were lower in the older women ($P = 0.04$). [Reprinted with permission from N. A. Klein *et al.*: *J Clin Endocrinol Metab* 81:2742–2745, 1996 (100). © The Endocrine Society.]

15–20 IU range (which is very similar to usual perimenopausal levels), and her estradiol levels were over 2000 pmol/liter. Endometrial thickening of more than 14 mm and endometrial hyperplasia were documented. On ovarian ultrasound, seven cystic structures ranging in size from 5–21 mm were seen instead of only one dominant follicle and its cyst, which would usually be present. Inhibin levels were in the normal range and LH levels were suppressed (128). Therefore, the clinical description of this woman with raised FSH levels because of a pituitary tumor suggests that mild elevations of FSH can cause multiple follicles to be recruited that produce high levels of estrogen and endometrial hyperplasia.

Strong cross-sectional evidence suggests that FP inhibin levels decrease during the perimenopause, based on the population-based study by Burger and colleagues (31). This is especially true in comparison to published normal ranges from the same laboratory (32, 33), as has recently been noted (86). It would be useful to reanalyze sera from the Melbourne Women's Midlife Health Study in the more specific N. Groome assay system used to detect dimeric inhibin B (100). Despite many questions about the cellular origins of inhibins A and B, and the characteristics and normal ranges of different inhibin assays, it is clear that perimenopausal inhibin levels are lower than premenopausal levels. They probably also decrease over time beginning before periods become irregular in the perimenopause; however, prospective data are necessary to confirm that hypothesis.

Why do inhibin levels appear to decrease in the perimenopause? There is no current explanation for this suggestion. Perhaps it is a biological characteristic of the more centrally located follicles that move outward as the outer follicles are stimulated and regress. There may be changes in as yet unknown paracrine factors. And, as in most other aspects of physiology, it is likely that there are hereditary differences that impact on ovarian inhibin production. Whatever the reason, lower levels of inhibin appear to indicate a decrease in the reserve of follicles that can be stimulated (117, 125). The best hypothesis for explaining the endocrinology of the perimenopause is that luteal phase inhibin levels (or reserves, perhaps specifically of inhibin B) become low before the absolute number of potentially responsive follicles has decreased. This allows FSH levels to rise and in turn results in what is descriptively termed "endogenous perimenopausal ovarian hyperstimulation." The resulting perimenopausal "syndrome" may include breast tenderness and enlargement, fluid retention, heavy, prolonged, or unpredictable menstrual bleeding, new onset of migraine headaches, and new or unpredictable mood swings. These symptoms, however, are far less dramatic, and the estradiol levels are lower (117) than during the extremely serious iatrogenic "ovarian hyperstimulation syndrome" that occasionally complicates IVF.

B. Five hypothesized phases of the perimenopausal transition

This review has documented an extreme variability of ovarian hormone levels in women in the transition into menopause. In addition, the early anecdotal reports and several epidemiological studies suggest an amazing array of symptoms that some perimenopausal women may experience. Some integration of this collected data into a postulated temporal series of changes would provide a framework for future research and some guidance (until prospective population-based studies are completed) for the clinician and the

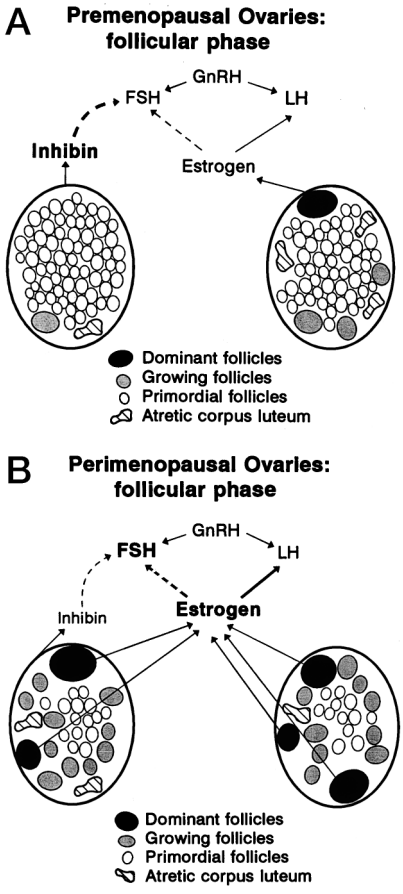

FIG. 7. These two stylized diagrams depict relationships between the two ovaries, the pituitary, and the hypothalamus during the early FP in ovaries from a premenopausal woman (*above*) and from a perimenopausal woman (*below*). Feedback inhibition is depicted by *dashed lines*, and *solid lines* indicate positive relationships or hormonal productions. Note the increased numbers of growing or dominant type follicles in the perimenopausal ovary and the lack of FSH suppression despite high levels of estrogen. The decreased inhibin secretion is postulated to cause this change in regulation of ovarian folliculogenesis.

perimenopausal woman. This section includes an effort to produce a hypothetical timeline for all of these observations and documented hormone levels based on prospective studies by Brown (102), Collett and associates (56, 57), Treloar (48), and Vollman (16), and cross-sectional data by Burger *et al*. (31), Santoro *et al.* (34), and Lenton and colleagues (49, 129) integrated with prospective population-based studies by Kaufert and associates (40, 71) and McKinlay *et al*. (45). The first necessity is to understand that any physiological transition that spans an average of 4 yr is likely to have differing characteristics during various parts of that period of time. Because menstrual cycle intervals and women's experience of symptoms are fundamental aspects of the clinical entity of perimenopause, they were used to divide the perimenopause into five postulated phases as shown in Table 3. Although estimated durations have been included, these may be sufficiently variable between women that no clear predictions are possible.

Phase A of the perimenopausal transition is postulated to be a time of regular and ovulatory cycles with increased

TABLE 3. Proposed phases of the perimenopause: clinical and hormonal characteristics

	Phase A	Phase B	Phase C	Phase D	Phase E
Duration	2–6 months	2–6 months	1–2 yr	1–2 yr	1 yr
Menstrual cycles	Regular, ovulatory shorter cycles, short follicular phases	Regular, often ovulatory disturbances	Irregular, alternate short and long cycles, ovulation less than 50%	Oligoamenorrhea, rare ovulation	Amenorrhea
Flow	Increased or the same	Increased	⇑ or less, often alternating	Spotting alternating with flooding	None
Menstrual cycle-related symptoms	↑ PMS ↑ Dysmenorrhea, breast symptoms, exacerbation of headaches and migraines	⇑PMS, intermittent dysmenorrhea	Less PMS but erratic, menstrual-type cramps may occur any time	No predictable symptoms, menstrual-like cramps in a few women, anytime	Few or confusing without subsequent flow
Vasomotor symptoms	First onset, cyclic before flow or midcycle (very often in the early morning)	Cyclic still during or at the end of sleep	Still cyclic, but less predictable, onset in daytime	Erratic, more persistent in long cycles	May become consistent daily, or decrease
Hormonal characteristics	Normal FSH, ↑ E_2 short follicular phases, LH normal, ? inhibin low	↑ FSH intermittent, ↑ E_2 at flow for some nonovulatory cycles, LH normal, ? inhibin low	Normal alternating with high E_2 ↑ FSH persistently, ↑ LH occasionally, ? inhibin low	↑ FSH, ↑ LH, E_2 normal except intermittent prolonged high levels, inhibin low	⇑FSH, ⇑LH Normal or low E_2, but intermittent low or high levels, below assay inhibin sensitivity

PMS, Premenstrual symptoms; E_2, estradiol; ↑ moderately increased; ⇑, very high.

breast tenderness, mood swings, fluid retention, and premenstrual symptoms. As shown by Santoro *et al*. (34) (Fig. 3), changes that are hormonally distinct compared with premenopausal women occur before cycles become irregular. Many women will notice shorter cycles as noted by Treloar, Vollman, and others. Often the FP is short. During this phase of the perimenopause, early morning night sweats (VMS) commonly are first experienced. Estradiol levels are at least intermittently high during this phase. Weight gain, migraine headaches, and abnormally heavy or flooding menstruation may occur. FSH levels are intermittently in the early FP but are usually normal. It is likely that inhibin levels would already be low.

During Phase B, perimenopausal women are likely to continue to have basically regular cycles but disturbances of ovulation (such as short luteal phase, luteal phase insufficient, and anovulatory cycles) become more common. Again, episodes of heavy flow may occur, premenstrual symptoms and dysmenorrhea are increased, and VMS may predictably return or increase in the days just preceding flow. FSH is now intermittently elevated but still only during the early FP. LH continues to be normal and estradiol is often high. Inhibin levels are probably inappropriately low.

Phase C is the beginning of what is now considered the onset of the perimenopause with unpredictable flow and alternating short and long or skipped cycles. Estradiol levels are intermittently quite high but may also be normal and sometimes low. VMS are postulated to begin to occur more commonly during the waking hours during this phase of the transition, although most women will have minor symptoms. For some women, night VMS become more persistent but continue to be cyclic before flow and may still predict flow in some cycles. By this phase, FSH levels are usually at least slightly elevated. LH levels may occasionally be increased during this phase. Inhibin levels are low.

Phase D is postulated to include the onset of oligomenorrhea, and more VMS, but may yet have times of high estrogen signs and symptoms after longer periods without flow. Ovulation occurs less than 50% of the time and often is abnormal in progesterone levels, if it does occur. By this phase, flow is usually light but unpredictable. Heavy flow during one menstruation may predict the onset of oligomenorrhea. FSH is now persistently elevated and LH also becomes consistently increased. Inhibin levels are postulated to be clearly low.

Phase E begins with the final menstrual period and includes the year after what is retrospectively defined as menopause by the WHO (10). This is a time of increased intensity and frequency of VMS, although a few women who experienced them earlier may also find they disappear. However, premenstrual type symptoms and cramps are usually less but sometimes occur without any subsequent flow. Breast, fluid, and mood symptoms decrease. FSH and LH are high and estrogen levels low or normal. Inhibin levels are consistently low.

This theoretical time course, as can be seen (Table 3) includes remarkably variable hormonal patterns. The actual time, menstrual cycle patterns, hormone levels, and women's experiences for each of the phases of this proposed timeline will need to be documented in appropriate prospective studies in population-based samples of women. Some women may also appear to be perimenopausal and then apparently recover ovarian/pituitary function for a time. The percentage of women experiencing this pattern has not yet been documented.

IX. Hormonal Physiology of Clinical Changes in the Perimenopause

The health concerns of women, their medical "complaints," and the public health issues related to menopause center around the menstrual cycle changes, VMS, risks for bone loss, and the emotional symptoms that sometimes occur during the perimenopausal transition. Although breast cancer may have one of its two peaks in incidence during and perhaps related to the high estrogen levels in the perimenopausal years (38), and despite the reported heart disease risks that appear to increase during the perimenopause (28), prospective data on the endocrinology of these two conditions in population-based studies are not sufficient for a clear review at this point in time. Therefore, breast cancer and coronary heart disease risks will not be included here.

Although reports of the perimenopause before the "estrogen deficiency era" report flooding menstruation, increased cervical mucus, breast tenderness, and emotional symptoms (52), and some of the anecdotal (130) and early epidemiological literature (40, 55, 71) can be interpreted to show high estrogen levels, nothing yet written has integrated women's experiences with the endocrinology of this transition. What follows will be a brief discussion of some of the symptoms reported by perimenopausal women in parallel with their hypothesized hormonal etiologies.

A. Endocrinology of menstrual flow and cycle-related symptoms

Menstrual flooding was one of the most distressing symptoms reported by midlife women in the Manitoba study (67). It was the reason for a physician visit in 25% of those seeing their doctor during the perimenopause. McKinlay *et al*. (45) likewise noted that 20% of doctor visits related to concerns about abnormal flow. Kaufert and colleagues (40), using factor analysis, identified flooding menstruation to be highly correlated ($r = 0.68$, $P < 0.01$) with a change from regular to irregular cycles. Likewise, heavy flow was a reported symptom in 51% of women studied by Neugarten and Kraines (55). Oldenhave and co-workers (43, 131) speculated that menorrhagia occurred "more often" than 20% in "premenopausal anovulatory cycles." Likewise, Shideler *et al*. (104) noted that a high estrogen level at the start of flow was associated with heavy flow. This observation was confirmed by Ballinger *et al*. (65) who found heavy flow was significantly associated with high estradiol levels in the fourth week of the cycle. The prevalence of menorrhagia was 45% in women in the early perimenopausal period and 48% in the late perimenopause as defined by Ballinger and associates (65).

The Melbourne Women's Midlife Health Study paper on perimenopausal symptoms does not mention menstruation (50) although reported flow characteristics were used as a method of classification of women into five groups (31). This is a strange omission given the prominence of abnormally

increased vaginal bleeding just noted in many reports concerning perimenopausal women. Likewise, the papers reporting on the Massachusetts Women's Health study rarely mention flow. This tendency to downplay vaginal bleeding in the perimenopause is more directly expressed by Santoro and colleagues (34): "We consider menses a less reliable marker of ovarian activity than hormones." Based on the evidence in this review, however, and the endocrinology of the perimenopause that is characterized by high mean estrogen levels and anovulatory cycles, it seems inappropriate to divorce vaginal bleeding from the menopausal transition.

Short cycles, short FPs, heavy flow (including clotting and flooding menstruation), midcycle spotting, and possibly an increased incidence of dysmenorrhea are all probably caused by high levels of estrogen (Table 1). These high estrogen levels are likely caused by endogenous perimenopausal ovarian hyperstimulation as previously proposed. It is also probable that the thickened endometrium shown in older women (Fig. 5), with or without local lesions such as polyps or submucous fibroids, predisposes to heavy flow (98). Anovulation coupled with high estrogen levels would further increase the risk for dysfunctional uterine bleeding as occurs with adolescent anovulatory cycles (83).

As has previously been discussed (in *Section IV.C*), the Kuopio study reported that the peak incidence of hysterectomy was between ages 46 and 48 (46), the age at onset of irregular periods, and thus the perimenopause in a population-based prospective study (45). It is not yet known whether the higher mean estradiol levels shown in the FP and premenstrually relate to the coincidence of hysterectomy and perimenopause onset. In addition, anovulation is prevalent in the perimenopause and often associated with persistent and abnormally high estrogen excretions (132–134). For this reason, appropriate therapy for menorrhagia, or menometrorrhagia in a woman in or approaching perimenopause, may be cyclic progesterone (oral micronized progesterone or medroxyprogesterone) on days 14–27 of the cycle in doses sufficient to effectively counterbalance high endogenous estrogen levels (135). (Note that, for women with cycles of 24 days or less, cyclic progesterone should be begun on day 10 and continued for 14 days.) Should abnormal bleeding persist despite increasing the doses of progesterone or medroxyprogesterone, androgen-derived progestins such as norethistrone or norgestrol will usually provide effective therapy. These progestins, however, cause significant reductions in high-density lipoprotein cholesterol (136) and, therefore, would not be ideal first-line therapy for midlife women in whom cardiovascular risks are already increasing (29). The reliance on gynecological surgeries (D & C, endometrial ablation, hysterectomy) to treat these perimenopausal bleeding patterns may be inappropriate given new understandings of the roles that ovulation disturbances and high estrogen productions related to endogenous perimenopausal ovarian hyperstimulation may play in their pathogenesis.

B. Vasomotor symptoms (VMS) in the perimenopause

Most Western physicians and women define menopause as beginning when VMS occur for the first time. Perhaps this classification is because these sudden episodes of subjective hot feelings and diaphoresis are commonly considered to be "classic symptoms of estrogen deficiency" (137). "Of the various sequelae resulting from the cessation of ovarian function, the occurrence of hot flashes is by far the most frequent. . . " (138). [It is worth noting that women in other countries and from different cultures report far fewer or less intense hot flashes and often do not even have a name for the experience (72). It is beyond the scope of this review to speculate on this observation and the reasons for it, which may include differences in genetics, diet, and even the status of women in the culture.]

VMS (meaning both day and night time episodic flushing and sweating) epidemiology and physiology have recently been extensively reviewed by Kronenberg (139). She tabulated published epidemiology studies showing that VMS occur in 11–60% of menstruating perimenopausal women (139). Although Kronenberg clearly states that hot flushes are "a phenomenon of women who *are in the transition to*, or have become menopausal" (139), most physicians believe VMS imply low estrogen levels and are therefore synonymous with established menopause. However, the current equation of VMS with low estrogen had already been shown (admittedly with crude data) to be incorrect by 1935! That year Fuller Albright (140) wrote: "Hypoestrinism has been shown not be a direct cause of the vasomotor phenomena." Likewise, in a prospective study documenting both hormone levels and a score for VMS intensity recorded over 12 yr across the perimenopause, Rannevik and associates (84) said, "There was no correlation between the severity of vasomotor symptoms and the levels of E_2. . . " However, this study did find (without showing the primary data) that VMS "inversely correlated to the decrease in E_2 around the menopause" (141). These observations do not negate the efficacy of estrogen therapy for VMS (142, 143). However, they do indicate that the relationships between estrogen levels and VMS are more complex than directly inverse with low estrogen levels.

Perimenopausal endocrine changes (reviewed in *Section V*) include intermittent times of high estrogen, elevated mean estradiol levels (Table 1), and ovulation disturbances. How does this information fit with the knowledge that VMS often begin in regularly menstruating women during the early years of the perimenopausal transition? Phrased another way: Can hot flushes occur when estrogen levels are high? The answer is yes, based on the data in two very different physiological studies (137, 144) that will be described in detail.

Bider and colleagues (144) were treating six normally menstruating infertile women with GnRH agonist (GnRHa) to assess pituitary function before planned IVF. They began treatment with injected estradiol benzoate immediately after first performing GnRH testing followed by a GnRHa test. Estrogen was injected weekly thereafter in a dose that changed the serum estradiol from 110 pmol/liter at baseline to the high level of 1011 pmol/liter. Hot flushes began about a week after the first estrogen injection at a time when, without therapy, estrogen levels would have fallen (144). However, the VMS began and continued during a time when estrogen was consistently high and equivalent to MCP levels (144).

A second study also documents that VMS may occur despite persistently high estrogen levels. Gangar and colleagues studied symptomatic menopausal women attending a menopause clinic (137). Women were scheduled to receive 50 mg estradiol implants every 6 months. However, because women began to complain of VMS before 6 months had elapsed, the 12 tested women had received their last previous implants of 50–200 mg estradiol at an average interval of 4 months (range 2–7). At the point at which women next experienced a recurrence of symptoms of "flushes, sweats, mood swings, and irritability," levels of estradiol were 1450 to >3500 pmol/liter. These estradiol levels were clearly supraphysiological (137). Although these authors concluded that "tachyphylaxis" (*e.g.*, a kind of tolerance requiring higher and higher doses to achieve a given effect) to estrogen accounted for their observation, Ginsburg and Hardiman (145) wrote a letter to the editor clarifying that VMS are triggered by "oestrogen withdrawal" rather than simply being caused by low estrogen levels.

Estrogen withdrawal, or rapidly decreasing estrogen levels, as a cause for VMS appears highly plausible and likely explains some or all of perimenopausal women's experiences. This postulate would fit all of the current data if three corollary conditions are added: 1) the higher the immediately preceding estrogen level, the greater the likelihood of provoking VMS; 2) the shorter the time period of, or the greater the withdrawal slope of estrogen levels, the more intense the VMS; and 3) previous exposure of the hypothalamus to high estrogen levels (for an unknown duration) is necessary before decreasing estrogen levels would cause VMS. These conditions would all be met during the postpartum period. Some women clearly do experience VMS immediately after childbirth. It is not known why all women do not develop postpartum VMS, except that progesterone as well as estrogen levels are high during pregnancy. That differs from the perimenopause in which estradiol levels are often high, but progesterone levels are normal or low.

There are important emerging relationships between undesirable premenstrual symptoms and hot flushes or night sweats. As an example of swinging and high but not low estrogen levels causing VMS, Casper and colleagues (146) reported in passing that 72% of 120 premenopausal women with severe premenstrual syndrome experienced VMS. VMS were documented (by skin temperature and conductance measures) in two cycles from one young women with premenstrual symptoms. Her VMS occurred during times within the menstrual cycle when estradiol levels should normally be dropping: after the midcycle estrogen peak in one cycle and just before menstrual flow in both cycles (146) (Fig. 8). Dennerstein and colleagues (50) noted that women who reported past premenstrual syndrome experiences were more likely to develop VMS during the final perimenopausal year. In a later analysis of 453 women participating in the Melbourne Midlife Women's Health longitudinal trial, a significant relationship (with odds ratio of 1.42; confidence interval of 1.04–1.93) between earlier reports of premenstrual symptoms and current experience of VMS was documented (85). Forty-seven percent of women with a history of premenstrual complaints reported VMS compared with 32% of women without that history (85). Estradiol and inhibin levels

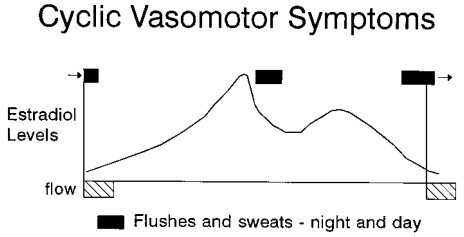

FIG. 8. This stylized diagram shows cyclic VMS (flushes and sweats) in relationship to the changing estradiol levels across an idealized menstrual cycle. The times of menstrual flow are shown as *hatched areas*. Note that VMS (shown as *black bars*) occur cyclically over several days before and during menses and for a shorter time after the midcycle estradiol peak.

were not different but FSH levels were higher in the women with VMS compared with those without (85). The association of distressing premenstrual symptoms with VMS may explain why regularly menstruating women over 45 yr of age with VMS who were participating in the population-based study from a Rotterdam suburb had a high likelihood of reporting a disturbed sense of well-being compared with those without VMS (odds ratio, 4.8; confidence interval, 2.3–9.7) (147).

Is there a physiological explanation for the association between premenstrual symptoms and vasomotor instability? Premenstrual symptoms and premenstrual syndrome have been shown to occur when higher estradiol levels are present in premenopausal women (148). The association of high estrogen with premenstrual symptoms has recently been confirmed both prospectively within women and cross-sectionally in women who differed in prospectively recorded premenstrual symptoms (149). Thus, women who experienced high estrogen during the early stages of the perimenopause (and consequentially breast, fluid, and mood premenstrual symptoms) appear to be more likely to experience withdrawal VMS later in the perimenopausal transition.

To date, no study in perimenopausal women has prospectively documented all of the variables that are necessary to understand these complex relationships: VMS occurrence, frequency, severity, and timing in relationship to physical and emotional experiences, hormone levels, and to menstrual flow. Kronenberg mentioned that 7 of the 500 women she surveyed wrote a comment in the margins of the questionnaire stating that they experienced flushes they felt were cyclic or related to flow (139). Women in phases A and B of the perimenopause (Table 3) commonly report VMS occurring before, and often as a reliable predictor of, menstrual flow (39)(Fig. 8). The cyclic VMS, which typically begin very early in the menopausal transition, also seem to differ from those experienced later in the perimenopause. These early VMS typically occur during sleep, often in the early hours of the morning, are associated with few or no daytime VMS, are often preceded by an aura (which may include anxiety, anger, or panic feelings), and are commonly associated with nausea, palpitations, dizziness, or faint feelings. Midcycle VMS (as shown by Fig. 8) appear to occur less commonly than do premenstrual ones (146) and might be postulated to be more likely in anovulatory cycles in which progesterone secretion does not immediately follow the high estrogen

levels. [This hypothesis is based on the evidence that progesterone is effective in VMS prevention and therapy (150, 151)].

VMS appear to be central to women's experience of the perimenopausal transition, yet they are very poorly documented. For example, typical studies investigate whether or not hot flushes or night sweats occur or the number experienced in a day. In contrast, what is important about VMS is both *when* they occur (especially if they waken a woman from sleep) and how intense they are. VMS, as mentioned earlier, are negatively related to women's sense of well-being, especially in the early perimenopausal and later menopausal years (147). As a graphic illustration of the importance of VMS, the only study of the risk for falling in perimenopausal women noted that women with flushes were more likely to fall (and therefore were at greater risk for fractures) (152). VMS are also associated with sleep disturbances (142), which may play a causal or even central role in perimenopausal women's decreased sense of well-being. On the other hand, women may report experiencing VMS and state that they are not bothered by them. In either case, VMS need to be described in better detail: when they occur in the perimenopausal transition, their relationship (if any) to vaginal bleeding, and their number and intensity during a waking or sleeping 24-h day (153). To understand the physiology of VMS and determine their relationship to women's experiences and well-being, they need to be meticulously documented prospectively in a population-based study.

In summary, VMS commonly start when estrogen levels are high and erratic in the early perimenopause [and occur during premenopausal years in women with PMS and frequent high estrogen levels (149)]. They are highly associated with a decreased quality of life (147), especially when they disturb sleep (40, 41). VMS have also been associated with an increased risk for falling (152) and with osteoporosis (131). Understanding the physiology of VMS and developing a range of nonhormonal and hormonal strategies for their control are important priorities in perimenopause research.

C. Perimenopause and the risk for osteoporosis

The risk for osteoporosis is one of the major reasons for recommending ovarian hormonal therapy to menopausal women (12, 154). For women, the terms "bone loss" and "menopause" have come to be said in the same breath as though they were synonymous. Numerous cross-sectional studies in selected populations appear to show an onset of bone loss at the average age of menopause (155–157). But, when does bone loss actually begin? Like studies of bone change in premenopausal women, that depends on the method of measurement [using, for example, quantitative computed tomography, dual energy absorptiometry (DXA), single energy absorptiometry (SPA) of radius or calcaneus, or radiogrammetry of the metacarpals], the site and architecture of the bone being measured, and the design of the study (158). Leaving aside those considerations, the determination of when bone loss begins can most accurately be ascertained by observational prospective studies. Although full publications on the prospective data are not available for the study currently ongoing in Hull, United Kingdom (141), or for the Melbourne Women's Midlife Study (159), preliminary prospective bone density data have been obtained from the authors. These data have been collated with other prospective information below.

1. Bone information from cross-sectional studies in the perimenopause. Several recent cross-sectional studies, including the population-based studies in Allegheny County, Pennsylvania (160, 161), and the Kuopio OSTPRE study from Finland (46, 162–164), are important to review. The Pennsylvania study, called Women's Healthy Lifestyle Project, enrolled 470 healthy premenopausal women who had menstruated within the preceding 3 months and measured vitamin D receptor status (a genetic characteristic recently associated with risk for osteoporosis), assessed life-style, and measured bone mineral density (160). In 334 women lean and fat mass measurements were made using the whole body DXA (160). That study showed lean body mass (muscle) was important in the prevention of bone loss (160), as were exercise, obesity, and dietary calcium intake, while the presence of the vitamin D receptor restriction site specified as "bb" was negatively associated with spinal bone density in this cross-sectional study in perimenopausal women (161).

The design and plan of the Kuopio study were described earlier in *Section IV.C*. Briefly, this 100% sample of women ages 45–56 in an entire province obtained a 93% response rate and 13,100 women completing questionnaires concerning whether or not and in what part of their body they had sustained fractures in the preceding 10 yr. This population averaged a BMI of 26 and consumed an average of 820 mg/day of calcium from dairy foods; 12% smoked and less than half reported regular physical activity. Eight percent of women with menstrual flow (within 6 months) and 12.5% of the menopausal women had experienced a fracture in the preceding 10 yr ($P = 0.0000$) (46).

Bone mineral density (BMD) by DXA of the spine and hip was measured in 1600 women in the Kuopio study sampled in a stratified random manner from the original cohort. Before this sampling, women with diseases or medications known to affect bone were excluded. (Oral contraceptives surprisingly were not a reason for exclusion, but hormonal replacement therapies *were*.) This sample of the population averaged 53.2 yr in age with an average BMI of 26.3; 529 of these women, whose average age was 51.2 yr, were still menstruating. The mean spinal DXA in the group was 1.130 ± 0.157 g/cm^2 while the femoral neck BMD was 0.932 ± 0.123 g/cm^2 (163). In both regions, the BMDs of menopausal women were lower than those of perimenopausal women even when corrected for age. Despite extensive life-style and morphometric investigations (excluding other DXA sites) only 18.7% of the spine and 25.4% of the hip BMD variance could be explained by measured variables including menopausal status. Menopausal status was a significant contributor to multiple regression equations for both spine and proximal femur (163). Life-style variables such as smoking, coffee consumption, calcium intake, and physical activity level did not statistically predict the spine BMD, but grip strength and alcohol intake both made significant positive contributions (163). Physical activity, weight, and age as

well as menopausal status were related to the femoral neck BMD (163).

The question that is most crucial to answer is whether or not a *given* woman is at risk for fractures. In the Kuopio perimenopausal (OSTPRE) study, a 2-yr prospective report documented that women in the lowest quartile for spine BMD had an incidence of fracture of 31.6 per 1000 person years compared with an incidence of 12 per 1000 person years for women in the highest two BMD quartiles (162). Furthermore, a spine BMD predicted the typical wrist fracture associated with menopause with an odds ratio of 1.8 (CL 1.29–2.46) and predicted rib fracture with an OR of 2.4 (CL 1.6–3.6) (162).

A final recent cross-sectional investigation studied women from three outpatient clinics near Sao Paulo, Brazil (165). This study measured bone density by DXA in the hip and spine in 417 healthy women (as documented by a medical history and physical examination) who ranged in age from 20–79 yr (165). Perimenopausal women were defined as those with oligomenorrhea of less than 1 yr duration. The average BMI for women in the decades of 40–59 yr was 25.0, mean lumbar spine BMD was 1.08, and femoral neck BMD was 0.86 g/cm^2 (165). Regression of spine BMD against age in perimenopausal women required a separate line with a slope of −0.66%/yr compared with a slope of −0.39% for the menopausal women. The women who were regularly cycling were described by a regression with no slope (165).

2. Prospective studies of bone density change in the perimenopause. Although large cross-sectional population-based studies provide some information about decade-related differences in bone density, the only informative data about bone change during a long and variable hormonal transition such as the perimenopause require prospective monitoring. Three prospective studies of radial bone density, as measured by single photon absorptiometry (SPA), include 2, 5, and 12 yr of follow-up, respectively (84, 166, 167). The first study measured radius SPA in 103 women in placebo groups for a therapy trial and the second in a convenience sample of 217 Caucasian women from a rural community in the United States of whom 89% participated (166, 167). The third study was a population-based sample from Malmo, Sweden, including 152 women of an original cohort of 192 who maintained participation for 12 yr (84). The Danish study showed that placebo-treated women experienced approximately 4% loss of bone mineral content at the radius over the 2 yr of study (2646). The US study showed that the women who were perimenopausal during the study lost an average of 5.6 ± 7.0% of their radial bone density during 5 yr *vs.* a loss of 8.4 ± 5.7% for women already menopausal at the study onset. Wide variations among individuals make these rates of bone loss not different (167). In the Swedish study the radius data are presented only sketchily with a frequency graph indicating losses of less than 5% to more than 40% with the average being 20%, not differentiated by menopausal status. Perhaps because of the variability of estradiol levels in perimenopausal women, only after menopause did estradiol relate to the rate of change in radius BMD (84).

In contrast to the scant prospective BMD data for the radius, more studies using measurements of the spine by dual energy methods (DPA and DXA) have been performed. Before describing these studies, it is important to note the omission of an important 2-yr prospective study by Recker and colleagues of 75 menstruating women over age 46 (average 49) who were enrolled with premenopausal levels of estradiol and FSH at the outset (168). This study was excluded because it was impossible to determine which of the women were pre- or perimenopausal (except for five who became menopausal during the study) (168). That study showed no significant overall change in spinal BMD by DPA measured every 6 months (168). In addition, two large dose-ranging studies of the new bisphosphonate, alendronate, have been excluded because, although they included some perimenopausal women who were 6 months from their last menstrual flow, the BMD change in the placebo groups were not broken down by rates in the late perimenopausal *vs.* early menopausal women (169, 170). These two studies include 90 placebo-treated women whose mean age was 51.4 (169) and 502 whose mean age was 53 in Stratum I of the "EPIC" study for prevention of bone loss with alendronate in postmenopausal women under 60 yr of age (170). However, thanks to S. A. Steel and D. W. Purdie of the North Humberside Osteoporosis Screening Project (141), and J. R. Guthrie and P. R. Ebeling of the Melbourne Women's Midlife Health Study, who are each performing prospective studies that are still acquiring data or have not yet been published, important prospective BMD data are available as unpublished communications.

Including the data from the two population-based, but as yet unpublished, studies from England and Australia, a total of 10 studies of spinal bone change by DPA or DXA are summarized in Table 4 (141, 171–177). Together, these combined data provide rates of spinal BMD change across 1–8 yr of observation on 335 perimenopausal women whose data can often be contrasted with simultaneously studied premenopausal (n = 319) or menopausal (n = 758) women. As can be seen, however, only a few studies used population-based samples. In several cases demographic data were unavailable—where it has been reported, BMI has been listed and ranges from 21.7 [in the Pouilles study in which women with a BMI > 24 were excluded (173)] to 24.7 in the Melbourne study.

The data shown in Table 4 document that, in the 7 of 10 studies for which control premenopausal and menopausal control data are available, the perimenopausal rate of spinal BMD loss exceeded that of women in the early menopause. To appropriately compare rates of change among different groups, a Fisher's combined *P* test (30) was used. The rate of spinal BMD change in 267 perimenopausal women (from the studies in which variance was available) was numerically greater than in 695 menopausal controls (−1.83% per yr *vs.* −1.29% per year; Fisher's F = 34.16, df = 16, $P = 0.0052$).

Similar evidence of increased perimenopausal bone loss in the femoral neck and the Ward's area were also present in the prospective data (171–177). In the shortest study, which examined a 1-yr rate of change (175), the only bone site whose rate of change was significantly different in perimenopausal women compared with premenopausal controls was the Ward's area of the proximal femur. Cross-sectional, age-stratified data published only as an abstract (178) also sug-

gested that the Ward's area (which contains a preponderance of trabecular bone) was most sensitive to change in menstruating women in their forties. Therefore, in summary of these various studies, the rate of spinal (and sometimes femoral) bone loss in the perimenopause exceeds the rate in early menopause as well as in the premenopausal years (which would be expected).

These data are surprising because bone loss has long been equated with low estradiol levels and with a lack of menstrual flow. As has been documented (Tables 1 and 2), the perimenopausal period includes times of erratic and normal or high, but not consistently low, estradiol levels and of unpredictable, but not absent, menstruation until what is eventually the final flow. Ovulation disturbances and therefore low progesterone levels are also typical of the perimenopause (15, 16, 84). It is postulated that in perimenopausal, as in premenopausal, women (101, 158), lack of consistent, normal ovulation is associated with accelerated bone loss. Finally, the increased rate of bone loss in the perimenopause may relate to elevated levels of cortisol secondary to major sleep disruption, emotional stress, and the socio-cultural transition that is the perimenopause in this culture (179).

3. Bone marker changes and the perimenopause. The physiology of the perimenopausal increased rate of spinal bone loss (as depicted in Table 4) should be revealed by the several cross-sectional or prospective studies of changes in bone markers in the menopausal transition (159, 167, 171, 172, 180–183). These studies are characterized by the use of a wide variety of bone resorption markers beginning with hydroxyproline and calcium (Ca) excretions corrected for creatinine to more specific excretions of Type I collagen products such as pyridinolines, and N- and C-terminal cross-linked telopeptides (NTx, CTx) both bound and free.

The largest population-based study to date, the Melbourne Women's Midlife Health Study, although still only reporting cross-sectional data, showed that NTx, as a sensitive marker of bone resorption (184), increased by 24% during the perimenopause without the expected coupling-related increases in bone formation markers such as bone-specific alkaline phosphatase and human osteocalcin (159). These authors asserted that "bone loss occurs before a decrease in (FP) serum sex hormone concentrations" and that NTx positively correlated with gonadotropin levels (159).

4. Quantitative bone ultrasound studies in the perimenopause. Two studies of quantitative ultrasound transmission through bone in perimenopausal women have been published. The first, from Hyogo, Japan, used transmission ultrasound through the patella in a convenience sample of 160 women ages 20 to 80 (185). In 19 perimenopausal women, the apparent velocity of ultrasound through bone was significantly faster than in the 28 menopausal women ($P < 0.02$) although the two groups did not differ in age nor in BMD by DXA (185). The second perimenopausal ultrasound study used the calcaneal broadband ultrasound attenuation (BUA) as measured by the Walker-Sonix instrument in 1000 consecutive consenting women ages 45–49 in the Aberdeen Osteoporosis Screening Study (186). Because DXA measurements of the spine and femur were available for correlation, as were assessments of height, weight, and menopausal status, ultrasound could be tested for its sensitivity and specificity as a screening tool. It was judged that BUA was a poor predictor of either spine or hip BMD with only 44% of women with spine BMD in the lowest quartile having the lowest quartile for BUA (186). Subsequently, both fracture and falling prediction publications have come from the Aberdeen Osteoporosis Screening Study (152, 187). It would be of great importance to determine from prospective data the sensitivity and specificity of ultrasound in predicting fractures in perimenopausal women.

Some evidence suggests that ultrasound reflects the architectural and structural characteristics of bone. That would be preferable to the purely mineral determinations obtained with DXA or other bone density measures. If rates of bone loss are accelerated during the last perimenopausal years, as a consequence of high bone resorption without increased formation, trabecular integrity may be breached (188). If ultrasound is able to detect these microarchitectural changes, it may provide a sensitive predictor of fracture risk in the perimenopause. The Japanese data suggest that this may be the case (185). Calcaneal ultrasound using a portable "dry" system (Concordant, International Medical Research, Ottawa, Ottawa, Ontario, Canada) is currently being obtained in a large population-based prospective study of men and women 25 to 80 yr of age in the Canadian Multicentre Osteoporosis Study (CaMOS) (189, 190). Women and men ages 40 to 60 at baseline are scheduled for a 3.0-yr prospective study in which ultrasound as well as BMD will be repeated. The yearly surveillance for fractures and the large number of likely perimenopausal women studied (~1500) should allow an assessment of the role of ultrasound in identifying those women at highest risk for fracture.

5. Falling and fractures in the perimenopause. Two prospective studies of fracture and falling in perimenopausal women ages 45–49 have been published in women from the Aberdeen, Scotland Osteoporosis Screening Study (152, 187). In addition, several papers reporting cross-sectional and retrospective fracture data from the ongoing Kuopio Osteoporosis Screening and Prevention Study have recently been published (46, 162–164). The rate of fracture in perimenopausal women (designated as "premenopausal" by the authors) with a mean age of 50 was 7.65 per 1000 person years, while in the menopausal women it was 17.4 per 1000 person years. In recalling any fractures since age 15, 17.7% of women reported experiencing at least one with the most frequent sites being wrist and ankle. The vast majority of fractures occurred during falls. In a bivariate analysis, menopause was associated with an increased number of fractures, and in a multivariate analysis parity decreased, and menopause increased, the risk for fractures (46).

Both studies show that perimenopausal fractures are more prevalent, a result that had been expected. The 2-yr incidence of fractures in 1857 women was 44 in the Scotland study (187). The odds ratio for a fracture was 4.55 (confidence interval, 1.5–13.50) if the spine DXA was in the lowest quartile ($P < 0.01$) (187). Also, perimenopausal women were more likely to fall than were pre- or postmenopausal women (152).

TABLE 4. Annual percentage changes in spinal dual energy (x-ray or photon) absorptiometry from prospective studies in perimenopausal women

Reference	Study (publication yr)	Duration (yr)	Perimenopausal (n)	Population	BMI	Age (range)	Premenopausal % change (n)	Perimenopausal (% change)	Menopausal % change (n)
171	Nilas and Christiansen (1989)	2–3	9	Selected from a population based study	ND	(45–54)	−0.15 ± 2.29(28)	−2.52 ± 1.9	−2.36 ± 4.24(50)
198	Elders *et al.* (1989)	2	45	Random sample	24.5	(46–55)	ND	−3.25 ± ?	−3.7 ± ?(40)
173	Pouilles *et al.* (1993)	2	42	Menopause clinic and random sample	21.7[c]	(45–66)	−0.79 ± 0.18 SEE (71)	−2.35 ± 0.22 SEE	−1.61 ± 0.38 SEE (117)
174	Tsunenari *et al.* (1995)	2	6	Selected (hospital workers)	21.8	(38–67)	+0.231 ± 1.61(34)	−2.72 ± 1.79	−0.74 ± 2.43(24)
175	Perrone *et al.* (1995)	1	25	Menopause clinic	ND	(45–55)	−1.5 ± 0.5(33)	−1.5 ± 0.5	−2.5 ± 0.7(24)
176	Ruiz *et al.* (1995)	2	49	Patients	22.3	(41–55)	ND	−3.0 ± 0.25(SE)	−1.0 ± 0.25(SE)(203)
177	Slemenda *et al.* (1996)	2–8	28	Newspaper advertising	ND	(30–77)	+0.32 ± 1.1(96)	−0.3 ± 1.51	−0.24 ± 1.7(73)
199	Iki *et al.* (1996)	2	8	Rural population	22.9	(35–70)	−0.01 ± 0.5(35)	−2.4 ± 0.54	−0.85 ± 0.21(122)
159[a]	Ebeling *et al.* (1996)	4	100	Random sample of population	24.7 ± −0.7	(46–55)	+0.5 ± 0.5(22)	−0.77 ± 0.7	−0.8 ± 0.3(42)
141[b]	Purdie *et al.* (1996)	5	23	Random sample of population	ND	(50–54)	ND	−1.69 ± −?	−0.72 ± ?(87)
Total Number of Women-Perimenopause			335				319		758
Data Summary - % spinal bone change by midlife classification (8 studies)									
Perimenopause: n = 267 −1.83 ± 4.49%/yr									
Fisher's F = 34.16; df = 16,34.16; $P = 0.0052$									
Menopause: n = 695; −1.22 ± 3.14%/yr									

ND, No data; SEE, standard error of the estimate.
[a]Personal communication from P. Ebeling and J. R. Purdie, Melbourne, Australia, 1997.
[b]Personal communication S. Steel and J. R. Purdie, from Hull, U.K., 1997.
[c]Excluded participants with BMI >24.

Past fractures were also predicted by low spinal or femoral BMD in perimenopausal women (46, 164). The fracture incidence (retrospectively determined over the preceding 10 yr and verified by medical reports) was significantly less in premenopausal women than in menopausal women (7.65 *vs.* 17.4 per 1000 person years) (46). One difficulty with both of these studies, however, is that they have not carefully separated the menstrual cycle characteristics of the participants so it is difficult to know which are truly pre-, peri-, or menopausal (46, 152, 162–164, 187). It is also important, although these are well designed epidemiological studies, that the major emphasis be placed on the prospective data and an even and unbiased assessment of fractures across the populations (191).

In summary, increasing numbers of women have been enrolled in population-based prospective studies of bone change, risk factors, and fracture incidence during the perimenopause. The present data indicate that the most rapid rate of spinal bone loss occurs before menopause during the years of the late perimenopause. This bone loss appears to be associated with increased bone turnover without the expected increase in bone formation markers and to be accompanied by both an increased risk for fractures and perhaps an increased risk for falling. Many variables including hereditary ones (maternal hip fracture and hip axis length), life-style (exercise, calcium intake, and cigarette, caffeine, or alcohol abuse) menstrual cycle (estradiol levels, changing estradiol levels, ovulation prevalence and luteal phase length, and cycle intervals) and morphometric variables (muscularity, body fat, and body weight) may be cofactors in the bone loss in the perimenopausal period. Prospective studies will be needed to document the subtle relationships about which only speculation is currently possible.

D. The endocrinology of perimenopausal psychosocial and emotional experiences

The perimenopausal period is known to be a complex sociocultural as well as a hormonal event (41, 72, 179). Part of the stress reported by Western women is clearly culture specific (17). However, the end of predictable menstruation, as occurs during the perimenopause, may be important to a woman simply because it is a *change*, no matter how aging and the end of reproductive life are viewed by that woman and by her culture (192). Whether or not the adjustment to this change causes emotional symptoms and help-seeking or illness behaviors will depend on that woman's own characteristics and the meanings attached to menopause in her culture.

As a review of endocrinology, it is appropriate to ask whether there are any hormonal links between the reported emotional experiences of perimenopausal women and the erratic and often high estrogen levels of the menopausal transition. Rather than equating affective symptoms with psychopathology, recent evidence suggests that increases in stress hormones (and probably symptoms that are stress related) are physiologically linked with high estrogen levels. A double-blind placebo-controlled study of 100 μg transdermal estradiol in young men documented that the estradiol-treated men experienced enhanced pituitary, adrenal,

and sympathetic responses before, during, and after a standardized psychosocial stress test (193). All of the young men (who were asked to speak and do arithmetic in front of a group) had increases in ACTH, cortisol, and norepinephrine levels as well as heart rates. However, as shown in Fig. 9, men who had been exposed to transdermal estradiol for 24–48 h before the test had significantly greater stress-related increases in ACTH and cortisol levels and showed a greater area under the norepinephrine curve. They also had an increased but nonsignificantly greater heart rate compared with those in the placebo group (193).

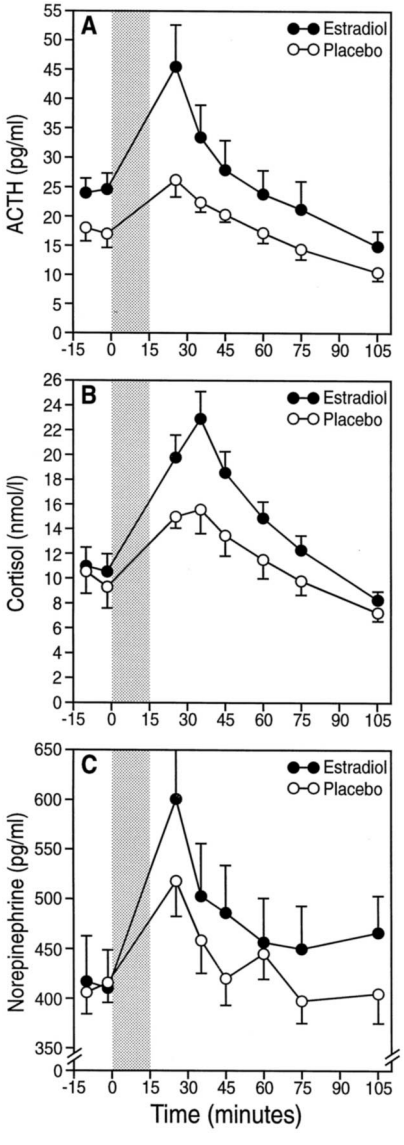

FIG. 9. This composite three-part diagram shows the mean (±SEM) ACTH levels (A), salivary cortisol levels (B), and serum norepinephrine levels (C) before and after a standardized stress test (*shaded area*) in young men randomized to wear a 100-μg estradiol patch for 24 to 48 h (n = 16, *closed circles*) or a placebo patch (n = 16, *open circles*). The stress-related increased ACTH and cortisol levels were significantly greater in the estradiol-treated men ($P < 0.001$ and <0.002, respectively), and the area under the norepinephrine response curve was also greater in the estradiol-treated group ($P < 0.05$). [Reprinted with permission of C. Kirschbaum *et al.*: *J Clin Endocrinol Metab* 81:3639–3643, 1996 (193). © The Endocrine Society.]

Based on the accentuated hormonal stress responses induced by short-term estradiol exposure and the series of observations summarized below, it is a reasonable hypothesis that a major component of the reported perimenopausal emotional distress may be causally related to high and erratic estradiol levels. However, any potential relationship of higher estrogen levels with emotional symptoms will not be further supported or proven untrue until women's reported anxiety, depression, frustration, and other psychological experiences are documented in parallel with physical, menstrual cycle, and hormonal events. Simultaneously recorded physical experiences, such as menstrual flow, cervical mucus, fluid or breast symptom change data, are not currently available.

In support of a causal relationship between high estradiol levels and women's perimenopausal concerns are the similarity to those experienced by teenagers (55) and by women with the premenstrual syndrome (148). Ballinger *et al.* (65) reported that women who had abnormal scores on psychometric tests early after menopause had *higher* estradiol levels than those with lower scores (65). In prospective, physiological studies of women reporting severe PMS, estrogen levels are correlated with the intensity of symptoms (148). A randomized, placebo-controlled menopause treatment study administering standard doses of conjugated equine estrogen (0.625 mg/day), which significantly improved sleep, also showed an estrogen-related increase in "inward directed hostility" (142). The irritability and mood swings reported by Gangar *et al.* (137) in women with VMS and implant-related high estradiol levels can also be attributed to the high estradiol exposure, rather than to menopause, *per se*.

Finally, given the associations of emotional symptoms with high estradiol levels, it is not surprising that cycling perimenopausal women whose estrogen levels are at least intermittently extremely high (31, 34, 104) would experience unwanted emotional symptoms. The term "mood swings" used commonly by women may be literally true and linked to wide fluctuations in estrogen levels. Thus the perimenopause and its resulting loss of fertility and social status (179) are coupled with erratic and high estrogen levels which, in addition to causing breast tenderness, fluid retention, and troublesome menstrual cycle bleeding, also increase the physiological responses to stress (193).

X. Summary and Necessary Research

This review of the perimenopause documents its complexity as a hormonal and socio-cultural transition. Early FP FSH levels increase, and short luteal-phase cycles and anovulation become prevalent. However, mean estradiol or estrogen excretion levels are not low. The perimenopause is characterized by higher average (compared with premenopausal women) and erratic estrogen levels. For example, mean early FP estradiol levels (averaging 225 ± 98 pmol/liter) significantly exceeded those found in young fertile women. Estradiol levels preceding flow are also higher in perimenopausal than in premenopausal women.

A hypothesis to explain the high estradiol levels, elevated FSH, and inconsistent ovulation postulates that lower inhibin levels (especially in the premenstrual portion of an anovulatory cycle) allow an increase in the early FP FSH level. This high FSH, in turn, stimulates a larger than normal number of ovarian follicles, and each stimulated follicle produces more estradiol. The resulting prolonged high or erratic estradiol levels, coupled with ovulation disturbances including anovulation, probably explain many of the morbidities associated with this phase in a woman's life: menorrhagia, breast tenderness, breast enlargement and fibrocystic breast problems, increased PMS, migraine headaches, increasing fibroid size, and risks for hysterectomy (± ovariectomy). This review proposes a new name for the signs and symptoms of high estrogen levels that some perimenopausal women experience: "Perimenopausal Endogenous Ovarian Hyperstimulation Syndrome." This name was chosen because, in hormone levels and pathogenesis, the perimenopausal state is similar to exogenous ovarian hyperstimulation therapy used for infertility treatment.

Paradoxically, despite elevated estradiol levels, the perimenopause is associated with a significant rate of spinal BMD loss. Early studies suggest that this loss exceeds that during the early menopausal period. Although this relationship had previously been documented (173), combined data from 10 studies provide increasing statistical evidence that significant, almost 2% per year, spinal bone loss occurs in the year before and after the last flow. These data require a reevaluation of the concept equating low estrogen levels with bone loss. Detailed prospective studies are needed that include measurements of bone changes in parallel with assessments of estradiol, progesterone, ovulation, menstrual cycles, weight (fat and muscle) changes, diet (calcium and Vitamin D), bone resorption and formation markers, and both the hormonal and the experiential aspects of stress.

The difficulty in defining the onset of the perimenopause will likely not be resolved until a longitudinal study of the perimenopausal transition is performed that includes women's prospectively recorded experiences in parallel with their hormonal, cycle interval, and ovulation characteristics. Although studies of menstrual cycle intervals, hormone levels, ovulation frequency, and women's symptoms and experiences have each been performed, no study combines all assessments. Such a study would need to extend over a long period of time to encompass a woman's last premenopausal years and to continue until 12 months have elapsed without flow. From data currently published, it is not evident that this lack of information is being rectified by the several important ongoing prospective studies [Melbourne Women's Midlife Health Study, the new National Institutes of Health-funded Study of Women Across the Nation (SWAN) (194)], or the osteoporosis studies in Kuopio, Finland, Hull, United Kingdom, or Malmo, Sweden).

The currently conducted Canadian Multicentre Osteoporosis Study (CaMOS) (189, 190), which has completed its recruitment of approximately 7,000 women ages 25 to over 80, in nine centres across Canada, has the potential to document the perimenopausal transition in a population-based sample of women. Serum samples have, so far, been obtained in only one center. However, CaMOS is now ready to begin a 3-yr interim data collection for women (and men) who were ages 40–60 at baseline. A 5.0-yr prospective assessment is planned for the entire cohort including about 3000 men. In addition to a detailed questionnaire (demographics, dietary, heredity, diet, reproductive history, quality of life) a Daily Perimenopause Diary has been developed and pilot tested (39). This instrument is similar to both the Menstrual Cycle Diary (195) (including flow characteristics, dysmenorrhea, and vaginal mucus) and to the Daily Menopause Diary (153) in documenting VMS by number and intensity occurring in both the night and day. Using data gathered with the Daily Perimenopause Diary, the CaMOS questionnaire, and bone assessments by DXA and ultrasound that are being documented, an improved understanding of the pathophysiology of perimenopausal bone loss is possible.

The perimenopause, in summary, is a unique hormonal transition. It is demonstrably more complex than it was previously understood to be; it is clearly not a time of "declining ovarian function" (11). Instead, dynamic perimenopausal ovaries produce erratic and high estradiol levels and rarely ovulate normally. These changes in hormonal levels manifest themselves in most aspects of a woman's health and may present as conditions involving almost every system of her body. Because the perimenopause is a time of high social and medical morbidity and is associated with significant costs for the health care system, it is important that research be conducted in impeccably designed prospective observational studies.

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