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Preface
Perimenopause

Ronald T. Burkman, MD
Guest Editor

The demographic characteristics of women within the United States continue to demonstrate substantial changes. In particular, the number of women entering the menopause continues to grow. For example, in 1990 about 10 million women entered the postmenopausal age group; by 2020, this number will almost double. During the transition from the reproductive time period to menopause, often defined as the perimenopause, the endocrine physiology is often unstable and unpredictable. Menstrual-related gynecologic symptoms become more common. In addition, women begin to have concerns about other health issues, such as osteoporosis, cardiovascular disease, and cancer. This issue of the *Obstetrics and Gynecology Clinics of North America* addresses many of these issues focusing on both the physiology of this transitional time period and the clinical problems. The authors in their reviews of the relevant literature not only provide an overview of the important data on many of these topics, but are also able to provide insights that will help clinicians care for women in this age group.

Dr Leon Speroff leads off the issue with a review of the definitions, the demography, and some of the physiology relevant to the perimenopausal portion of a woman's lifespan. Because the perimenopause involves a number of changes in endocrine physiology, it is important for clinicians to understand how steroids reach their target tissues and what factors modify their access to such tissues. Dr Geoffrey Hammond addresses this complex topic in his article. Equally important is an understanding of the metabolism of sex steroids, which is the topic of Dr Daniel Grow's article. The role that sex steroids, particularly estrogen, play in cognitive function and in the whole development of the female brain is a field of research that is rapidly growing. Drs Robert Green and Whitney Dixon

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provide a review of many of the key issues. The perimenopause can be challenging to clinicians because it is a time period when many women become symptomatic with gynecologic disorders for the first time in their life. Dr Andrew Kaunitz reviews this important topic providing advice regarding evaluation and treatment. Drs Janice Wagner, Jay Kaplan, and I review the preclinical data on the cardiovascular effects of reproductive hormones and draw some conclusions that could have clinical implications. Because declining endogenous estrogen levels are associated with accelerated loss of bone mass around the menopause, it is important for clinicians to understand the risk factors involved and the recommendations for screening and prevention. Drs Raja Sayegh and Phillip Stubblefield provide a comprehensive review of this topic. The effects of postmenopausal use of estrogens and progestins on a variety of neoplasias have been the subject of numerous observational studies and meta-analyses. Drs John Collins and James Schelesselman cover their effects on breast and endometrial cancer, and I review their effects on ovarian and colon cancer. A clearly important issue is the counseling approaches one uses to discuss many of these issues with women. Dr June La Valleur provides a practical overview of this important topic. The use of alternative or complementary approaches to manage symptoms that occur among women in this age group is important given the growing interest in these approaches in this country. Dr Maida Taylor reviews the available evidence regarding the effectiveness of many of these nontraditional, alternative therapies. Finally, although risk of pregnancy declines in the perimenopausal age group, pregnancy when it occurs is frequently unplanned and often results in pregnancy termination. Dr J. Kell Williams addresses the contraceptive issues and needs of perimenopausal women.

On behalf of my fellow authors, I thank Ms. Carin Davis and her associates at WB Saunders for all their assistance in putting together this issue. It is hoped that the articles effectively assist clinicians in addressing the various needs of perimenopausal women.

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The perimenopause
Definitions, demography, and physiology

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Changes in menstrual function are not symbols of some ominous "change." There are good physiologic reasons for changing menstrual function, and understanding the physiology reinforces a healthy, normal attitude. Attitude and expectations about the menopause are very important. Women who have been frequent users of health services and who expect to have difficulty do experience greater symptoms and higher levels of depression [1,2]. The symptoms that women report are related to many variables within their lives, and the hormonal change at menopause cannot be held responsible for the common psychosocial and lifestyle problems we all experience. Menopausal women do not suffer from a disease (specifically a hormone-deficiency disease), and postmenopausal hormone therapy should be viewed as specific treatment for symptoms in the short term and preventive pharmacology in the long term. Medical intervention at this point of life should be regarded as an opportunity to provide and reinforce a program of preventive health care.

Definition and hormonal characteristics of the perimenopausal transition

There has been considerable confusion in defining the perimenopausal transition. Data from longitudinal studies provide an objective designation that can be used to define and establish what is called the *perimenopausal transition*. The years before menopause that encompass the change from normal ovulatory cycles to cessation of menses are known as the *perimenopausal transitional* years, marked by irregularity of menstrual cycles. The best information comes from two longitudinal studies (with very similar results): the study of Vollman [3] of more than 30,000 cycles recorded by 650 women and the study of Treloar et al [4] of more than 25,000 woman-years in a little over 2700 women. The obser-

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vations of Vollman [3] and Treloar et al [4] documented a normal evolution in length and variation in menstrual cycles.

Menstrual cycle length is determined by the rate and quality of follicular growth and development, and it is normal for the cycle to vary in individual women. Menarche is followed by approximately 5 to 7 years of relatively long cycles, and then there is increasing regularity as cycles shorten to reach the usual reproductive age pattern. In the 40s, cycles begin to lengthen again. The highest incidence of anovulatory cycles is under age 20 and over age 40 [5,6]. At age 25, over 40% of cycles are between 25 and 28 days in length; from 25 to 35, over 60% are between 25 and 28 days. The perfect 28-day cycle is indeed the most common mode, but it totaled only 12.4% of Vollman's [3] cycles. Overall, approximately 15% of reproductive-age cycles are 28 days in length. Only 0.5% of women experience a cycle less than 21 days long, and only 0.9% a cycle greater than 35 days [7]. Most women have cycles that last from 24 to 35 days, but at least 20% of women experience irregular cycles [8].

When women are in their 40s, anovulation becomes more prevalent, and before anovulation, menstrual cycle length increases, beginning 2 to 8 years before menopause [4]. This period of longer cycles uniformly precedes menopause no matter the age when menses cease, whether menopause is early or late [9]. The duration of the follicular phase is the major determinant of cycle length [10,11]. This menstrual cycle change before menopause is marked by elevated follicle-stimulating hormone (FSH) levels and decreased levels of inhibin, but normal levels of luteinizing hormone (LH) and slightly elevated levels of estradiol [12–16].

Contrary to older belief (based on the report by Sherman et al [10]), estradiol levels do not gradually wane in the years before the menopause, but remain in the normal range, although slightly elevated, until 6 months to 1 year before follicular growth and development cease. The Sherman et al [10] data were from a small cross-sectional study of one cycle collected from 8 women, age 46 to 56. More recent longitudinal studies of women as they pass through the perimenopausal transition reveal that estrogen levels do not begin to decline until less than a year before menopause [16,17]. Indeed, women experiencing the perimenopausal transition actually have higher overall estrogen levels, a response that is logically explained by an increased ovarian follicular response to the increase in FSH secretion during these years [18,19].

As noted, most women experience a 2- to 8-year period of time before menopause when anovulation becomes prevalent [4]. During this period of time ovarian follicles undergo an accelerated rate of loss until eventually the supply of follicles is finally depleted [20,21]. In a study of human ovaries, the accelerated loss seemed to begin when the total number of follicles reached approximately 25,000, a number reached in normal women at an age of 37 to 38 [22]. This loss correlates with a subtle but real increase in FSH and decrease in inhibin. The accelerated loss is probably secondary to the increase in FSH stimulation. These changes, including the increase in FSH, reflect the reduced quality and capability of aging follicles, and their reduced secretion of inhibin, the granulosa cell

product that exerts an important negative feedback influence over FSH secretion by the pituitary gland. Both inhibin A and inhibin B may be involved. Luteal phase levels of inhibin A and follicular phase levels of inhibin B decrease with aging, and may antedate the rise in FSH [23–25].

The inverse and tight relationship between FSH and inhibin indicates that inhibin is a sensitive marker of ovarian follicular competence and, in turn, that FSH measurement is a clinical assessment of inhibin. The changes in the later reproductive years (the decline in inhibin allowing a rise in FSH) reflect diminishing follicular reactivity and competence as the ovary ages [13,14,17]. The decrease in inhibin secretion by the ovarian follicles begins early (around age 35), but accelerates after 40 years of age. This is reflected in the decrease in fecundity that occurs with aging. Furthermore, the ineffective ability to suppress gonadotropins with postmenopausal hormone therapy is a consequence of the loss of inhibin, and for this reason FSH cannot be used clinically to titer estrogen dosage.

The perimenopausal years are a time period during which postmenopausal levels of FSH (greater than 20 IU/L) can be seen despite continued menstrual bleeding, whereas LH levels still remain in the normal range. Occasionally, corpus luteum formation and function occur, and the perimenopausal woman is not safely beyond the risk of an unplanned and unexpected pregnancy until elevated levels of both FSH (> 20 IU/L) and LH (>30 IU/L) can be demonstrated [15]. Even under these circumstances, however, fluctuations can occur, with a period of ovarian failure followed by resumption of ovarian function [14,17]. Because variability is the rule, it is wise to recommend the use of contraception until the postmenopausal state is definitely established.

In the longitudinal Massachusetts Women's Health Study, women who reported the onset of menstrual irregularity were considered to be in the perimenopausal period of life [26]. The median age for the onset of this transition was 47.5 years. Only 10% of women ceased menstruating abruptly with no period of prolonged irregularity. The perimenopausal transition from reproductive to postreproductive status was, for most women, approximately 4 years in duration. In the study by Treloar [27], the average age for entry into the perimenopausal transition was 45.1, and the age range that included 95% of the women was 39 to 51. The mean duration of the perimenopausal transition was 5 years, with a range of 2 to 8 years. Averages for the perimenopausal transition are as follows [4,26,27]:

Average age of onset: 46
Age of onset for 95% of women: 39 to 51
Average duration: 5 years
Duration for 95% of women: 2 to 8 years

The age of menopause

Designating the average age of menopause has been somewhat difficult. Based on cross-sectional studies, the median age was estimated to be somewhere

between 50 and 52 [28]. These studies relied on retrospective memories and the subjective vagaries of the individual being interviewed. Until recently, studies with longitudinal follow-up to observe women and record their experiences as they pass through menopause were hampered by relatively small numbers. The Massachusetts Women's Health Study provides data from 2570 women [26].

The median age for menopause in the Massachusetts Study was 51.3 years. Only current smoking could be identified as a cause of earlier menopause, a shift of approximately 1.5 years. Those factors that did not affect the age of menopause included the use of oral contraception, socioeconomic status, and marital status. A median age of menopause means that only half the women have reached menopause at this age. In the classic longitudinal study by Treloar [29], the average age of menopause was 50.7, and the range that included 95% of the women was 44 to 56. In a survey in The Netherlands, the average age of menopause was 50.2 [30]. About 1% of women experience menopause before the age of 40 [31].

Clinical impression has suggested that mothers and daughters tend to experience menopause at the same age, and there are two studies indicating that daughters of mothers with an early menopause (before age 46) also have an early menopause [32–34]. There is sufficient evidence to believe that undernourished women and vegetarians experience an earlier menopause [32,35]. Because of the contribution of body fat to estrogen production, thinner women experience a slightly earlier menopause [36]. Consumption of alcohol is associated with a later menopause [33]. This is consistent with the reports that women who consume alcohol have higher blood and urinary levels of estrogen, and greater bone density [37–41].

There is no correlation between age of menarche and age of menopause [29,30,32,42]. In most studies, race, parity, and height have no influence on the age of menopause; however, two cross-sectional studies found later menopause to be associated with increasing parity [26,30,32,36]. Two studies have found that irregular menses among women in their early 40s predicts an earlier menopause [43,44]. A French survey detected no influence of heavy physical work on early menopause (before age 45) [45]. An earlier menopause is associated with living at high altitudes [46]. There is reason to believe that premature ovarian failure can occur in women who have previously undergone abdominal hysterectomy or endometrial ablation, presumably because ovarian vascular flow has been compromised [47,48]. And finally, earlier menopause is associated with growth retardation in late gestation [49].

Multiple studies have consistently documented that an earlier menopause (an average of 1.5 years earlier) is a consequence of smoking. There is a dose-response relationship with the number of cigarettes smoked and the duration of smoking [50,51]. Even former smokers show evidence of an impact.

Unlike the decline in age of menarche that occurred with an improvement in health and living conditions, most historical investigation indicates that the age of menopause has changed little since early Greek times [52,53]. Others (a minority) have disagreed, concluding that the age of menopause did undergo a change,

starting with an average age of about 40 years in ancient times [54]. If there has been a change, however, history indicates it has been minimal. Even in ancient writings, an age of 50 is usually cited as the age of menopause.

Hormone production after menopause

Shortly after the menopause, one can safely say that there are no remaining ovarian follicles [55]. Eventually there is a 10- to 20-fold increase in FSH and approximately a threefold increase in LH, reaching a maximal level 1 to 3 years after menopause, after which there is a gradual, but slight, decline in both gonadotropins [56,57]. Elevated levels of both FSH and LH at this time in life are conclusive evidence of ovarian failure. FSH levels are higher than LH because LH is cleared from the blood so much faster (initial half-lives are about 20 minutes for LH and 3 to 4 hours for FSH), and perhaps because there is no specific negative feedback peptide for LH like inhibin.

The postmenopausal ovary secretes primarily androstenedione and testosterone. After menopause, the circulating level of androstenedione is about one half that seen before menopause [58]. Most of this postmenopausal androstenedione is derived from the adrenal gland, with only a small amount secreted from the ovary, although androstenedione is the principal steroid secreted by the postmenopausal ovary [59]. Dehydroepiandrosterone and its sulfate, originating in the adrenal gland, decline markedly with aging; in the decade after menopause the circulating levels of dehydroepiandrosterone are approximately 70% less and levels of dehydroepiandrosterone sulfate are about 74% less than the levels in young adult life [60].

Testosterone production decreases by approximately 25% after menopause, but the postmenopausal ovary in most women secretes more testosterone than the premenopausal ovary. With the disappearance of follicles and estrogen, the elevated gonadotropins drive the remaining stromal tissue in the ovary to a level of increased testosterone secretion. Suppression of gonadotropins with gonadotropin-releasing hormone agonist or antagonist treatment of postmenopausal women results in a significant decrease in circulating levels of testosterone, indicating the gonadotropin-dependent postmenopausal ovarian origin [61–63]. The total amount of testosterone produced after menopause, however, is decreased because the amount of the primary source, peripheral conversion of androstenedione, is reduced. The early postmenopausal circulating level of androstenedione decreases approximately 62% from young adult life [60]. The menopausal decline in the circulating levels of testosterone is not great, from no change in many women to as much as 15% in others [16,57,60]. Nevertheless, compared with young women, the overall androgen exposure of perimenopausal women to androgens is less (Tables 1 and 2) [64,65].

The circulating estradiol level after menopause is approximately 10 to 20 pg/mL, most of which is derived from peripheral conversion of estrone, which in turn is mainly derived from the peripheral conversion of androstene-

Table 1
Blood production rates of steriods

	Reproductive age (mg/d)	Postmenopausal (mg/d)	Oophorectomized (mg/d)
Androstenedione	2–3	0.5–1.5	0.4–1.2
Dehydroepiandrosterone	6–8	1.5–4	1.5–4
Dehydroepiandrosterone sulfate	8–16	4–9	4–9
Testosterone	0.2–0.25	0.05–0.18	0.02–0.12
Estrogen	0.350	0.045	0.045

From Longcope, Jaffe W, Griffing G. Production rates of androgens and oestrogens in postmenopausal women. Maturitas 1981; 3:215; with permission.

dione [58,66,67]. The circulating level of estrone in postmenopausal women is higher than that of estradiol, approximately 30 to 70 pg/mL. The average postmenopausal production rate of estrogen is approximately 45 microgram per 24 hours, almost all being estrogen derived from the peripheral conversion of androstenedione. The androgen:estrogen ratio changes drastically after menopause because of the more marked decline in estrogen, and an onset of mild hirsutism is common, reflecting this marked shift in the sex hormone ratio. With increasing age, a decrease can be measured in the circulating levels of dehydroepiandrosterone sulfate and dehydroepiandrosterone, whereas the circulating postmenopausal levels of androstenedione, testosterone, and estrogen remain relatively constant [57,58].

Estrogen production by the ovaries does not continue beyond the menopause; however, estrogen levels in postmenopausal women can be significant, principally because of the extraglandular conversion of androstenedione and testosterone to estrogen. The clinical impact of this estrogen varies from one postmenopausal woman to another, depending on the degree of extraglandular production, modified by a variety of factors.

The percent conversion of androstenedione to estrogen correlates with body weight. Increased production of estrogen from androstenedione with increasing body weight is probably caused by the ability of fat to aromatize androgens. This fact and a decrease in the levels of sex hormone–binding globulin (which results in increased free estrogen concentrations) contribute to the well known association between obesity and the development of endometrial cancer. Body weight has a positive correlation with the circulating levels of estrone and estradiol [58]. Aromatization of androgens to estrogens is not limited to adipose tissue,

Table 2
Changes in circulating hormone levels at menopause

	Premenopause	Postmenopause
Estradiol	40–400 pg/mL	10–20 pg/mL
Estrone	30–200 pg/mL	30–70 pg/mL
Testosterone	20–80 ng/dL	15–70 ng/dL
Androstenedione	60–300 ng/dL	30–150 ng/dL

however, because almost every tissue tested has this activity. Eventually, the ovarian stroma is exhausted and, despite huge reactive increments in FSH and LH, no further steroidogenesis of importance results from gonadal activity.

With increasing age, the adrenal contribution of precursors for estrogen production proves inadequate. In this final stage of estrogen availability, levels are insufficient to sustain secondary sex tissues. In summary, the symptoms frequently seen and related to decreasing ovarian follicular competence and then estrogen loss in this protracted climacteric are as follows:

1. Disturbances in menstrual pattern, including anovulation and reduced fertility, decreased flow or hypermenorrhea, irregular frequency of menses, and then ultimately amenorrhea.
2. Vasomotor instability (hot flushes and sweats).
3. Atrophic conditions: atrophy of vaginal epithelium; formation of urethral caruncles; dyspareunia and pruritus caused by vulvar, introital, and vaginal atrophy; general skin atrophy; and urinary difficulties, such as urgency and abacterial urethritis and cystitis.
4. Health problems secondary to long-term deprivation of estrogen: the consequences of osteoporosis and cardiovascular disease.

During the menopausal years, some women experience severe multiple symptoms, whereas others show no reactions or minimal reactions that can go unnoticed. The differences in menopausal reactions in symptoms across different cultures are poorly documented, and indeed, it is difficult to do so. Individual reporting is so conditioned by sociocultural factors that it is hard to determine what is caused by biologic versus cultural variability [68,69]. For example, there is no word to describe a hot flush in Japanese, Chinese, and Mayan [70]. Nevertheless, there is reason to believe that the nature and prevalence of menopausal symptoms are common to most women, and that variations among cultures and within cultures reflect not physiology, but differences in attitudes, societies, and individual perceptions [71–74].

Vasomotor symptoms

The vasomotor flush is viewed as the hallmark of the female climacteric, experienced to some degree by most postmenopausal women. The term *hot flush* is descriptive of a sudden onset of reddening of the skin over the head, neck, and chest, accompanied by a feeling of intense body heat and concluded sometimes by profuse perspiration. The duration varies from a few seconds to several minutes and, rarely, for an hour. The frequency may be rare to recurrent every few minutes. Flushes are more frequent and severe at night (when a woman is often awakened from sleep) or during times of stress. In a cool environment, hot flushes are fewer, less intense, and shorter in duration compared with a warm environment [75].

In the longitudinal follow-up of a large number of women, fully 10% of the women experienced hot flushes before menopause, whereas in other studies as many as 15% to 25% of premenopausal women reported hot flushes [2,26,76,77]. The frequency has been reported to be even higher in premenopausal women diagnosed with premenstrual syndrome [78]. In the Massachusetts Women's Health Study, the incidence of hot flushes increased from 10% during the premenopausal period to about 50% just after cessation of menses [26]. By approximately 4 years after menopause, the rate of hot flushes declined to 20%. In a community-based Australian survey, 6% of premenopausal women, 26% of perimenopausal women, and 59% of postmenopausal women reported hot flushing [79]. Although the flush can occur in the premenopause, it is a major feature of postmenopause, lasting in most women for 1 to 2 years but, in some (as many as 25%) for longer than 5 years. In cross-sectional surveys, up to 40% of premenopausal women and 85% of menopausal women report vasomotor complaints [77]. In the United States, there is no difference in the prevalence of vasomotor complaints in surveys of black and white women [80,81].

The physiology of the hot flush is still not understood, but it apparently originates in the hypothalamus and is brought about by a decline in estrogen. Not all hot flushes, however, are caused by estrogen deficiency. Flushes and sweating can be secondary to diseases, including pheochromocytoma, carcinoid, leukemias, pancreatic tumors, and thyroid abnormalities [82]. Unfortunately, the hot flush is a relatively common psychosomatic symptom, and women often are unnecessarily treated with estrogen. When the clinical situation is not clear and obvious, estrogen deficiency as the cause of hot flushes should be documented by elevated levels of FSH.

The correlation between the onset of flushes and estrogen reduction is clinically supported by the effectiveness of estrogen therapy and the absence of flushes in hypoestrogen states, such as gonadal dysgenesis. Only after estrogen is administered and withdrawn do hypogonadal women experience the hot flush. Although the clinical impression that premenopausal surgical castrates suffer more severe vasomotor reactions is widely held, this is not borne out in objective study [83].

Although the hot flush is the most common problem of the postmenopause, it presents no inherent health hazard. The flush is accompanied by a discrete and reliable pattern of physiologic changes [84]. The flush coincides with a surge of LH (not FSH) and is preceded by a subjective prodromal awareness that a flush is beginning. This aura is followed by measurable increased heat over the entire body surface. The body surface experiences an increase in temperature, accompanied by changes in skin conductance, and followed by a fall in core temperature, all of which can be objectively measured. In short, the flush is not a release of accumulated body heat but is a sudden inappropriate excitation of heat-release mechanisms. Its relationship to the LH surge and temperature change within the brain is not understood. The observation that flushes occur after hypophysectomy indicates that the mechanism is not dependent on or caused directly by LH release. The same hypothalamic event that causes flushes also

stimulates gonadotropin-releasing hormone secretion and elevates LH. This is probably secondary to hypothalamic changes in neurotransmitters that increase neuronal and autonomic activity [85].

Premenopausal women experiencing hot flushes should be screened for thyroid disease and other illnesses [86]. Clinicians should be sensitive to the possibility of an underlying emotional problem. Looking beyond the presenting symptoms into the patient's life is an important service to the patient and her family that eventually is appreciated. This is far more difficult than simply prescribing estrogen, but confronting problems is the only way of reaching some resolution. Prescribing estrogen inappropriately (in the presence of normal levels of gonadotropins) only temporarily postpones by a placebo response dealing with the underlying issues. In an English randomized, placebo-controlled study of women being treated with estrogen implants and requesting repeat implants, there was no difference in outcome in terms of psychologic and physical symptoms comparing the women who received an active implant with those receiving a placebo [87].

Preventive health screening of healthy perimenopausal women

The most important thing a clinician can offer to the perimenopausal woman is the education she needs and desires to make therapeutic choices. This early educational process helps to build a solid relationship with patients, a relationship they will want to continue as they age. Clinicians should consider the following recommendations:

- Provide guidance and education to facilitate a patient's decision making.
- Provide time and an appropriate location for sensitive and uninterrupted discussions.
- Use educational materials, especially handouts, but also explain them using your own words.
- Involve family members during counseling and educational visits.
- Be accessible. Consider designating a member of your staff as the menopause resource person. Encourage telephone calls.
- Be involved in community and hospital educational programs for the public.
- Use an effective, well-trained counselor for patients who need in-depth help in coping with life's trials and tribulations.

Preventive intervention during the perimenopausal years has three major goals. The overall objective is to prolong the period of maximal physical energy and optimal mental and social activity. A specific goal is to detect as early as possible any of the major chronic diseases, including hypertension, heart disease, diabetes mellitus, and cancer, and impairments of vision, hearing, and teeth. Finally, the clinician should help perimenopausal women to traverse the menopausal period of life smoothly. Preventive health care and management of the later reproductive years give clinicians an excellent opportunity to function as a

woman's primary care provider. The issues of preventive health care are familiar ones. They include contraception; cessation of smoking; control of body weight and alcohol consumption; prevention of heart disease and osteoporosis; maintenance of mental well-being (including sexuality); treatment of urologic problems; and cancer screening. Management of the transition years should be significantly oriented to preventive health care.

A complete medical history and physical examination should be performed every 5 years, at about age 40, 45, 50, and 55. Annual visits should include a breast and pelvic examination, Pap test, screening for sexually transmitted diseases when appropriate, a thyroid-stimulating hormone assessment in the 40s and every 2 years beginning at age 60, and Hemoccult testing after age 50. Annual screening mammography should begin at age 40. At each visit, appropriate testing is scheduled for specific chronic conditions and indicated immunizations are provided. Counseling covers changing nutritional needs; physical activities; injury prevention; occupational, sexual, marital, and parental problems; urinary function; and use of tobacco, alcohol, and drugs.

Summary

The perimenopausal years should serve to remind patients and clinicians that this is a time for education. Certainly preventive health care education is important throughout life, but at the time of midlife, a review of the major health issues can be especially rewarding. The failure to respond appropriately (by either clinician or patient) easily leads to a loss of the patient from a practice, but equally, if not more importantly, is the probability that the loss of a patient from a practice means that another woman has lost her involvement in a preventive health care program. Contrary to popular opinion, the menopause is not a signal of impending decline, but rather a wonderful phenomenon that can signal the start of something positive, a good health program.

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Access of reproductive steroids to target tissues

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The access of natural and synthetic steroids to their target cells is influenced by anatomic, physiologic, and biochemical variables that are tissue-specific and in many instances is also influenced by physiologic state. They include differences in vascular supply, the anatomic position of target cells relative to blood vessels, the cellular and extracellular matrix composition of tissues in which target cells are located, and the interaction between steroids and their plasma transport proteins. These variables are often overlooked in the design or evaluation of treatments involving natural or synthetic steroids, which are being used increasingly as contraceptives by young women or for hormonal replacement in the elderly. This article examines these issues with special emphasis on the role that plasma steroid–binding proteins play in regulating the metabolism and actions of steroids that influence reproductive tissues in women.

Anatomic location of target cells and physiologic state

Steroids that are not bound by plasma proteins are free to diffuse from blood vessels into target tissues, but the extent to which this occurs varies considerably between tissues and is highly dependent on the type of vascular supply. For instance, the blood-brain barrier limits the access of steroids to target cells within the brain when compared with tissues where the vascular supply is much more pervasive (eg, uterus). In addition, physiologic state can influence vascular supply (eg, in the endometrium); blood flow and transit time (eg, in the skin); and cellular content of tissues (eg, breast). The vascular wall within the blood capillaries of different tissues also varies considerably; for instance, the vascular endothelial wall in most tissues is relatively impervious to plasma proteins,

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whereas it is highly fenestrated in the liver and allows plasma proteins freely to enter the tissue bed.

Once inside extravascular compartments of tissues, steroids must often migrate considerable distances to get to target cells, such as epithelial cells, in the absence of carrier proteins. To accomplish this, they traverse extravascular compartments that may include stromal cells and adipocytes, and must make their way through a complicated network of proteins within the basal lamina before they can gain access to epithelial target cells. Given the lipophylic nature of steroids, and their propensity to associate with lipid-rich plasma membranes, this presents considerable tissue-specific variables that influence their access to particular target cells. Steroids can passively diffuse into their target cells, and are then either metabolized or interact with specific nuclear hormone receptors, which act as ligand-dependent transcription factors to regulate the expression of particular subsets of genes to effect a cellular response [1]. There is a growing awareness that steroids may act by nongenomic mechanisms [2], however, which in some instances may involve interactions with cell surface receptors or signaling components within the extracelluar matrix [3,4]. The migration of steroids from blood vessels to their target cells is very tissue-specific, and presents challenges and opportunities that need to be considered in the design of new therapeutic strategies involving the use of exogenous steroids or steroid analogues.

Plasma steroid–binding proteins

Once steroids enter the bloodstream, as the result of secretion by an endocrine gland or after exogenous administration, they immediately interact with several plasma steroid–binding proteins, and a state of dynamic equilibrium is established that determines how they are distributed between the various protein-bound fractions and the non–protein-bound or free fraction. This is important because, according to the free hormone hypothesis, it is only the free fraction that is considered to be available for uptake by target tissues [5].

The plasma concentrations and biochemical characteristics of the main steroid-binding proteins in human plasma are listed in Table 1, and they fall into two categories: (1) high-abundance proteins with low steroid-binding affinity and specificity (albumin and orosomucoid); and (2) low-abundance proteins with high steroid-binding affinity and specificity (sex hormone–binding globulin [SHBG] and corticosteroid-binding globulin [CBG]). Although the affinity of albumin for all steroids is relatively low, it possesses some degree of steroid selectivity. For instance, its affinity for estradiol is greater than for testosterone and is more than an order of magnitude greater than for cortisol [6]. In patients with abnormally low plasma concentrations of SHBG or CBG, or who have a variant protein with reduced binding-affinity [7], the role of albumin in determining the amount of free hormone becomes significant. Its effect in this regard is steroid-specific, however, and this can be demonstrated readily in serum samples that have been heat-treated to denature the high-affinity binding proteins SHBG and CBG [8]. Under these

Table 1
Concentrations and Biochemical Properties of the Steroid-binding Protein in Human Plasma

Protein	Plasma concentration mg/L	Carbohydrate %	Stability at 60°C	Kd: at 37°C	Steroid-binding specificity
Albumin	40,000	0	+	2×10^{-5} M	estradiol* > testosterone >progesterone
Orosomucoid†	750	40	+	6×10^{-6} M	3-oxo-4-ene-steroids*
CBG	20	23	−	3×10^{-8} M	cortisol> progesterone*
SHBG	2	12	−	6×10^{-10} M	DHT> testosteorne> estradiol*

Abbreviations: CBG, corticosteroid-binding globulin; SHBG, sex hormone–binding globulin.
* Kd shown for these steroids;
† also known as α_1-acid glycoprotein.

conditions, the percentage of free cortisol (about 35%) in the heat-treated serum is substantially greater than that of estradiol (about 3%), and this reflects the differences in the affinity of albumin for these steroids.

There has been considerable debate about whether albumin-bound steroids are accessible to target tissues because of the relatively rapid dissociation of steroids from its binding sites [8]. Although this has never been demonstrated under steady-state physiologic conditions, steroids may be lost more readily from albumin than from the high-affinity binding proteins during their passage through blood vessels, and especially in tissues where the blood flow and transit time are high. This does not mean, however, that substantial amounts of albumin-bound steroid are available for tissue or target cell uptake, otherwise significant differences in the concentrations of steroid precursors would be observed in the venous blood draining large metabolically active tissues, such as the prostate, when compared with peripheral venous blood. Such an effect would be especially obvious in the context of those steroids that are predominantly albumin-bound, such as androstenedione [8], and this simply does not occur [9].

Like albumin, orosomucoid has a low affinity for steroids but displays some preference for biologically active steroids with a keto-group at their C3 position, such as testosterone and progesterone (see Table 1). Its plasma concentration is much lower than that of albumin, however, and any impact it has on regulating the plasma distribution of reproductive steroids is minor. The steroid-binding properties of both albumin and orosomucoid are essentially unchanged after serum samples are heat treated (60 °C), and this also distinguishes them from SHBG and CBG (see Table 1). This property can be exploited in measurements of the distribution of steroids between various protein-bound fractions and the free fraction in undiluted serum samples [8,10].

The plasma concentrations of SHBG and CBG are both much lower than those of albumin or orosomucoid (see Table 1), but they play a major role in binding and

transporting biologically active steroids in the blood because of their much greater steroid-binding affinities and selectivity. Their plasma concentrations also vary considerably under different physiologic conditions; during disease states; and in response to some drug treatments, including the use of exogenous hormones [11,12]. Although the impact that SHBG and CBG have on determining the metabolic clearance and distribution of their steroid ligands in the blood is considerable [8], the understanding of how these proteins function to regulate the access of reproductive steroids to their target cells is still limited. In the following sections, the different roles that SHBG and CBG may play in this context are reviewed in light of several recent discoveries in relation to their structure and function.

SHGB

The SHBG is a homodimeric glycoprotein that binds testosterone and estradiol with high affinity. It has generally been assumed that a single steroid-binding site is located at the SHBG dimer interface, but recent crystallographic and molecular biologic studies have shown that each subunit of the homodimer contains a functional steroid-binding site [13,14]. Thus, each SHBG homodimer may carry more than one type of steroid ligand. This information also means that measurements of SHBG steroid-binding capacity reflect the molar concentrations of SHBG monomer rather than that of the homodimer [13]. In addition to providing valuable information about how steroid ligands are coordinated within the human SHBG steroid-binding site [14], these crystallographic studies have revealed that SHBG is a zinc-binding protein [15]. This led to the discovery that occupancy of a zinc-binding site located close to the steroid-binding pocket influences its steroid-binding specificity, and results in a marked decrease in the affinity of SHBG for estradiol with no change in its affinity for androgens [15]. Although this effect only occurs at 0.1- to 1-mM zinc concentrations, it may impinge on the way the protein functions in specific locations, such as the male reproductive tract, where zinc concentrations are particularly high. In this context, it should also be noted that the *SHBG* gene is expressed in the testis where it gives rise to a product generally referred to as the *testicular androgen-binding protein*, which is thought to influence the development or maturation of sperm in the male reproductive tract. These and other new data that will emerge from further crystallography experiments will undoubtedly provide clues about how SHBG binds other biologically molecules, such as phytoestrogens and environmental contaminants that may affect the health of women [16] .

The primary function of SHBG is to transport biologically active androgens and estradiol in the blood, and it plays a key role in regulating the free fraction of these steroids that is considered to be biologically available to target cells [8]. This is influenced primarily at two levels: (1) through competition for available steroid-binding sites at anatomic locations where concentrations of endogenous or exogenous steroid ligands are particularly high; and (2) through fluctuations in

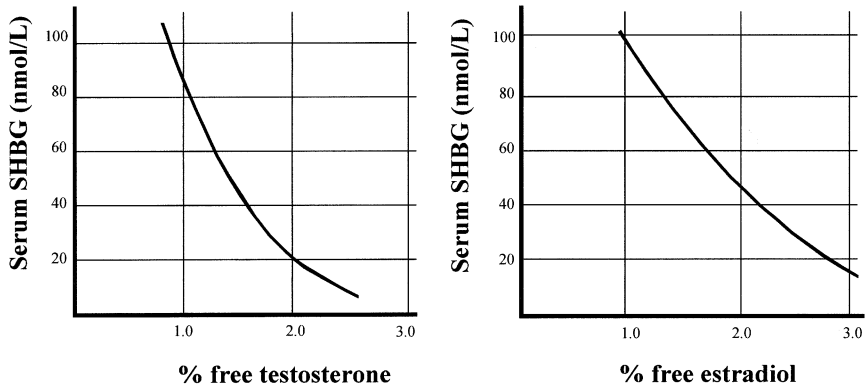

Fig. 1. Relationship between serum sex hormone–binding globulin levels and the percentages of non–protein-bound or free testosterone and estradiol in women. Linear relationships based on serum sex hormone–binding globulin levels determined using an immunoradiometric assay [61], and percentages of free steroids determined in undiluted serum samples using the centrifugal-ultrafitration dialysis method [63].

the plasma concentrations of SHBG (Fig. 1) that may occur under normal physiologic conditions, or as a result of drug treatment. These issues are considered later. In addition to the established role of SHBG in regulating the amount of hormone in the blood, there have been numerous reports indicating that SHBG plays a more active role in delivering steroids to target cells [17,18], and that it may actually mediate the nongenomic actions of its ligands through an interaction with a plasma membrane receptor [19]. According to the latter model, unliganded SHBG interacts with a plasma-membrane binding site on steroid-responsive cells within the human prostate [20,21], endometrium [22], and breast [23,24]. Plasma membrane-bound SHBG is able to interact with ligand, and SHBG dissociates from the receptor if this occurs, resulting in a signal transduction event that involves changes in intracellular cAMP levels [19,25]. Although the identity of this SHBG receptor and its physiologic significance remain obscure, several reports have indicated that SHBG can exit the blood circulation and enter the extravascular compartments of some tissues [17,26]. In addition to a possible interaction with a specific plasma membrane receptor, the presence of SHBG in extravascular compartments may regulate the migration and local access of its steroid-ligands to target cells that are not in the immediate vicinity of the blood supply.

Plasma SHBG is produced by hepatocytes [27,28], but very little is known about the molecular mechanisms responsible for regulating the expression of the human SHBG gene in the liver. It has been shown that a liver-enriched transcription factor, Hepatocyte Nuclear Factor (HNF)-4, plays a key role in determining the tissue-specificity of its expression [29], but our understanding about how the gene responds to a variety of hormonal and metabolic regulators is largely confined to studies of changes in plasma levels of SHBG [11] and is based

Table 2
Variables that influence plasma SHBG levels in men and women

Variable	Men	Women
Age	Increases slightly after 50 years	No change after menopause
Hyperthyroidism	Increase	Increase
Hypothyroidism	No change	Decrease
Obesity	Decrease	Decrease
Hyperandrogenism	—	Decrease
Hypoandrogenism	Increase	—
Estrogens	Increase	Increase
Levonorgestrel	—	Decrease

on assumptions that these changes reflect alterations in the expression of the *SHBG* gene in the liver. These assumptions may be largely correct, but some of these effects could also be brought about by changes in the metabolism or clearance of the protein.

The major factors that influence plasma SHBG levels are listed in Table 2. Among these, both estrogens and thyroid hormones stimulate the production and secretion of SHBG by human HepG2 hepatoblastoma cells [30]. On the other hand, androgens [11] and androgenic progestins [31] reduce plasma SHBG levels. The mechanism underlying the reduction in plasma SHBG levels in response to increased androgen exposure is less clear. It may involve a suppression of *SHBG* gene expression or an inhibition of estrogen-dependent effects that generally serve to enhance its synthesis. There are little if any fluctuations in plasma SHBG in women throughout the menstrual cycle, but body mass index is a major physiologic determinant of the blood levels of SHBG in both women and men [32,33]. Obesity is almost always associated with very low serum levels of SHBG, which increase progressively in response to weight loss [34]. Conversely, relative high serum SHBG levels are generally found in women with anorexia [35]. This inverse relationship between SHBG and body mass index could be related to increased insulin levels in obese individuals [33,34], especially because insulin seems to reduce SHBG production by HepG2 cells [36].

A common genetic polymorphism exists within the human *SHBG* gene, which results in a variant form of SHBG with an additional site for N-linked glycosylation [37]. This extra carbohydrate chain may influence the clearance of the variant protein [38], but does not seem to influence its function. Most recently, a polymorphism in a pentanucleotide repeat in the human *SHBG* promoter has been shown to influence its transcriptional activity in vitro [39], and it remains to be seen whether this contributes to individual variations in serum SHBG levels or the response of the *SHBG* gene to hormonal or metabolic regulators (see Table 2). Other variations in either the regulatory or coding regions of the *SHBG* gene probably exist, and these may in part explain the relatively wide range of serum SHBG levels (30 to 80 nM) in normal women. Knowledge of an individual's serum SHBG level might be an important pharmacogenomic parameter to consider in future strategies aimed at prescribing

an optimal replacement dose of natural estrogen. This is based on the simple assumption that women with inherently higher serum SHBG levels probably need a larger dose of estradiol to achieve the same amount of free estradiol in the blood, when compared with women with lower serum SHBG levels.

Throughout the human life cycle marked changes occur in the plasma levels of SHBG and its occupancy by reproductive steroids in both men and women, and these changes can be influenced further by exogenous hormone treatments (Fig. 2). Little is known about how plasma SHBG levels fluctuate during human fetal development but by analogy with studies in other animals [40], including a human *SHBG* transgenic mouse model [41], there is every reason to suspect that marked fluctuations in *SHBG* expression occur in the human fetal liver, and that this probably influences the exposure of the fetus to either androgens or estradiol during critical stages of development. In infants, concentrations of SHBG in the blood increase during the first weeks of life [42], perhaps as a result of stimulation of the expression of the gene by thyroid hormone, and remain at relatively high levels in boys and girls until puberty [43,44]. This may serve to limit the actions of small amounts of androgens and estradiol that originate from adrenal sources before the onset of gonadal steroidogenesis, and it is important to

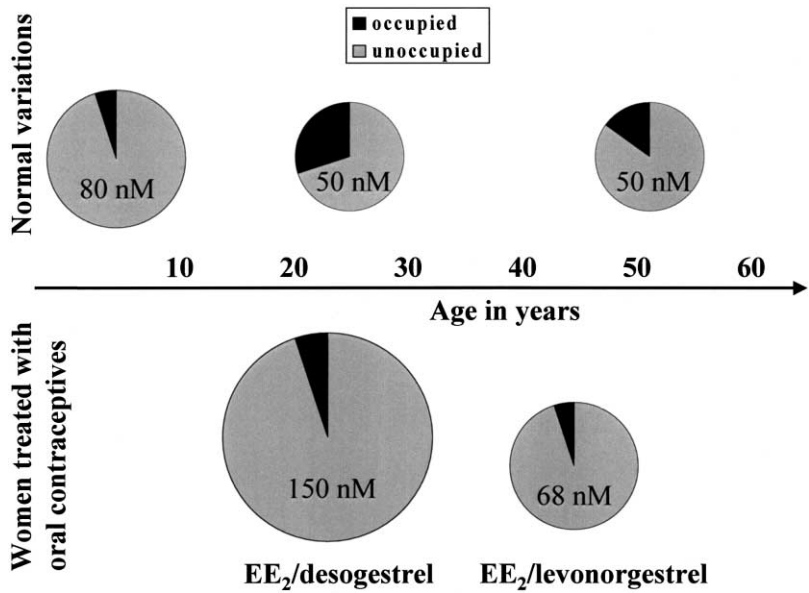

Fig. 2. Relative proportions of occupied and unoccupied sex hormone–binding globulin steroid-binding sites in human serum samples taken during different stages of the human life cycle, and in women after administration of oral contraceptive formulations [62]. Estimates for occupancy are based on serum sex hormone–binding globulin levels (shown as nM) measured under various physiologic conditions and after treatment with contraceptives containing ethinylestradiol in combination with either desogestrel or levonorgestrel, and the relative amounts of various steroid ligands bound by sex hormone–binding globulin.

note that the SHBG steroid-binding sites during this phase of life are essentially unoccupied, at least by steroids (see Fig. 2).

During puberty in boys there is a consistent and marked reduction in plasma SHBG levels [44], and this is accompanied by an increase in the occupancy of SHBG steroid-binding site, primarily as the result of the increasing production of testosterone by the testis. In contrast, reductions in plasma SHBG levels in girls during puberty are less pronounced, and may be related to changes in body mass, rather than gonadal steroid production [43]. As a result, the plasma SHBG levels are on average about two times greater in women than in men. Moreover, there is a clear gender difference in the occupancy of the SHBG steroid-binding sites: in men the lower serum SHBG levels and much higher testosterone levels equate to a much greater occupancy of the SHBG steroid-binding site than in women, even during their peak reproductive years.

In elderly men and women, serum SHBG levels change marginally in response to a combination of age-related hormonal and metabolic adjustments. In obese perimenopausal women, however, low plasma levels of SHBG and increased peripheral estradiol production in adipose tissue translate into a substantial elevation in unopposed free estradiol levels, which may contribute to the increased incidence of endometrial cancer in these women [45]. By contrast, normal weight or lean elderly women who have relatively high serum SHBG levels may be at greater risk for developing osteoporosis because their serum SHBG levels are relatively high and their serum free testosterone and estradiol levels are correspondingly low [46]. Modifications in either the serum levels of SHBG or the occupancy of its steroid-binding site therefore offer potential therapeutic opportunities in postmenopausal women.

Serum SHBG levels increase markedly in women treated with thyroid hormone and this certainly impacts on the plasma distribution of SHBG ligands and their access to target tissues. Exogenous estrogens, and particularly ethinyl estradiol, are the only other pharmaceutical agents that have such a marked effect on increasing serum SHBG levels [47]. In this case, the route of administration may be particularly important; for instance oral administration may be much more effective in this regard when compared with topical (eg, transdermal) administration. This is caused by differences in the exposure of the liver to the exogenous steroid, with the first pass effect of high concentrations of drug in the hepatic portal vein after uptake from an oral dose having the greatest impact. When progestins that bind SHBG with high affinity are coadministered orally with estrogen, this may have the additional effect caused by displacing endogenous hormones, such as testosterone, from the SHBG binding site in the hepatic portal vein, and thereby accentuating any androgen-dependent reductions in SHBG biosynthesis in the liver. When administered parenterally, the latter effect may be obviated because of relatively slow release of drug into the blood circulation, where the large numbers of unoccupied SHBG binding sites easily accommodate exogenous steroid ligands, and reduce the exposure of the liver to them considerably.

The administration of contraceptive steroid formulations that allow the estrogenic component to increase plasma SHBG to relatively high levels, while

maintaining minimal exposure to androgenic progestins, has other therapeutic benefits, some of which are probably related in large part to a marked reduction in the free levels of endogenous testosterone in the blood [48]. These include a reduction in androgen-dependent hair growth and acne [48,49]. This type of treatment results in large increases in serum SHBG levels, as well as, and the number of SHBG steroid-binding sites that are not occupied by known ligands (see Fig. 2). Finally, it is not known if the SHBG steroid-binding site is occupied by other biologically important endogenous ligands under normal physiologic conditions. If it is, there may be other unanticipated consequences of altering the way SHBG influences their balance in the body.

CBG

The CBG is the major transport protein for natural glucocorticoids in all mammalian species including humans [50]. Human CBG also exhibits a relatively high affinity for progesterone, danazol, and medroxyprogesterone, but it does not bind 19 other synthetic-progestins [51]. Like SHBG, its plasma levels increase in response to exogenous estrogen treatment [52,53], and CBG is perhaps a more reliable marker of estrogen action than SHBG because its basal serum concentrations are remarkably similar between individuals [54].

Although the *CBG* gene is expressed in several extrahepatic locations, the liver is the main site of plasma CBG synthesis [55,56]. The main function of CBG is to transport and regulate the bioavailability of glycocorticoids to a wide range of sites in the body where these steroids function to regulate developmental processes, maintain homeostasis, and control inflammation [50]. Human CBG is structurally very closely related to several members of the serine proteinase inhibitor superfamily, and interactions between CBG and specific proteinases destroy its ability to bind steroid [57,58]. This suggests that CBG provides a targeted release of its ligands to specific tissues in which these proteinases accumulate, such as at sites of inflammation or tissue remodeling [50].

Whatever mechanism CBG uses to regulate the access of its ligands to their target cells, it is also important to remember that human CBG has a single steroid-binding site that can bind both glucocorticoids and progesterone with high affinity. The anatomic location of CBG determines to a large extent its occupancy by specific steroids. For instance, in the ovary during the luteal phase of the menstrual cycle, or in the placenta, CBG functions predominantly as a progesterone-binding protein. In the context of the female reproductive tract, this could be important because human follicular fluid contains CBG, which seems to enhance the ability of progesterone to promote the acrosome reaction on human sperm [59], and the cumulus cells surrounding the oocyte produce both CBG and progesterone [60]. These observations suggest that CBG is somehow involved in the targeted delivery of progesterone to the acrosome, and this provides an example of how a steroid-binding protein that is normally found in plasma may serve to regulate the access of a particular ligand to a target cell that lies well outside the blood supply.

Summary

The access of reproductive steroids to their target cells varies considerably between tissues, and is influenced to a great extent by their interactions with plasma steroid–binding proteins, and with SHBG and CBG in particular. An increased awareness of how SHBG and CBG function within the blood circulation, and within extravascular compartments of steroid-responsive target tissues, needs to be incorporated into the design and evaluation of therapies involving the administration of both natural and synthetic steroids, which influence female reproduction and healthy aging.

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Metabolism of endogenous and exogenous reproductive hormones

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During the ovulatory menstrual cycle, estradiol is produced by the functioning ovary. Ninety-five percent of circulating serum estradiol originates from the ovary with the maturing follicle or corpus luteum. Estradiol production rates increase by at least fivefold from baseline in a natural ovarian cycle [1], with serum levels ranging from about 30 pg/mL during menses to about 200 pg/mL at ovulation. In contrast to estradiol, less than half of estrone is produced by direct ovarian secretion. Estrone is converted from estradiol by 17β-estradiol dehydrogenase in the liver and other tissues [2]. Estrone is also produced by the conversion of estrone sulfate to estrone by the adrenal, and by the aromatization of androstenedione whose concentration also peaks at mid-cycle.

There is a major decrease in serum estrogens in the perimenopause and in the immediate postmenopausal period [3] with little change occurring in the subsequent years. After the final menstrual period, there is very little ovarian contribution to serum concentrations of sex steroids. Women with a history of bilateral oophorectomy show little difference in serum levels of estrone, estradiol, or testosterone when compared with women undergoing a natural menopause [4]. Androstenedione levels were actually higher in women with oophorectomy that their menopausal cohort. This is perhaps counterintuitive [5], but highlights the very low metabolic activity of the postmenopausal ovary.

Estradiol and estrone in the menopause

Postmenopausal women have serum estradiol levels below 15 ng/mL and mean estrone levels of about 30 pg/mL [4]. Although estradiol levels are negligible in

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the menopausal ovary, it has been frequently observed that estrone levels are higher in older men and women than in younger adults. Older women convert androstenedione to estrone more efficiently than young women. In keeping with this observation, adipose tissue aromatase mRNA expression also increases twofold to fourfold between age 20 and 60 [6,7]. Adipose mRNA expression is highest in the hip fat and lowest in the abdomen [7]. Aromatase expression also occurs to a large degree in the skin, and to a lesser degree in bone, brain, and breast. Age and time since the final menstrual period are not significant predictors of sex hormone concentrations.

The degree of obesity is a major predictor for both estradiol and estrone. Estrone levels in obese women are on average 40% higher than in nonobese women with levels ranging from about 25 to 40 pg/mL. Estrone increases linearly with increasing weight [4]. Estradiol also increases with increasing body mass, with mean levels ranging from 3 to 6 pg/mL [4]. This is consistent with the fact that aromatization of androstenedione and testosterone to estrone and estradiol occurs principally in the adipose tissues and skin. Despite a doubling of estradiol with obesity, the clinical significance of these low levels is uncertain.

Cigarette smoking does not seem to impact the levels of either estrone or estradiol, but does raise serum levels of estrogen precursor, androstenedione [4]. Smoking does slightly increase hepatic metabolism of estrogen, but also slightly increases the production of sex hormone–binding globulin (SHBG) (decreasing free estrogen) and has little net effect on estrogen metabolism [8]. Smokers in general do not need special dosing considerations for menopausal hormone replacement therapy [9]. Increasing physical activity shows a negative correlation with both estrone and estradiol. This relationship persists even when controlling for obesity. Women who are most active (measured objectively or subjectively) had the lowest estrogen levels.

Physical activity did not predict levels of serum androgens. Increasing alcohol consumption tends to decrease both estrone and estradiol concentrations independent of the effects of obesity and smoking. Alcohol consumption does not seem to be related to the levels of circulating androgens [4].

Estrogen metabolism

All estrogens circulate in the blood with a high degree of protein binding. Estradiol is 38% bound to SHBG, 60% to albumin, with about 2% circulating in the free state [10]. Estrone, estrone sulfate, and estriol all have loose binding to SHBG, but greater affinity for albumin than estradiol. Each molecule of SHBG can accommodate one molecule of sex steroid (estrogen or androgen). SHBG concentrations increase with estrogen therapy, pregnancy, hyperthyroidism, and smoking, but decrease with androgen excess, hypothyroidism, obesity, and insulin resistance. Obese women have up to 30% less SHBG than their normal-weight peers resulting in this relative increase in estradiol.

Metabolic clearance rate

Metabolic clearance rate is defined as the volume of blood cleared of a substance in a unit of time. It reflects the extraction of a substance by tissues and varies according to blood flow. Tight binding of a hormone to a carrier molecule, such as SHBG or albumin (in the case of estrone sulfate), decreases metabolic clearance rate. The liver is the organ primarily responsible for estrogen metabolism, although a fair amount occurs in the skin and adipose tissues.

Estradiol and testosterone are similarly bound to carrier proteins, with 69% tightly bound to SHBG and 30% more loosely bound to albumin. Only 1% circulates freely. Estrone and androstenedione are more loosely bound, only 8% to SHBG, 85% or so to albumin, with a larger free fraction of about 5%. Estrone sulfate is very tightly bound to albumin [11]. Table 1 lists the metabolic clearance rates for the major estrogens.

Conversion of one estrogen to another occurs chiefly through 17β-hydroxysteroid dehydrogenase, which favors the oxidation of estradiol to estrone over estrone to estradiol by 17% to 4% for the reverse reaction [12]. Conjugation of both estradiol and estrone is chiefly through the sulfate reaction, with estrone sulfate being the chief eventual product. Estrone sulfate is tightly bound to albumin and has a low metabolic clearance rate. Ethinyl estradiol is also quickly sulfated, with rapid appearance of ethinyl estradiol sulfate in the circulation after ingestion [13].

The major natural estrogen metabolite in the urine is 3-methoxy-2-hydroxyestrone glucuronide. Ethinyl estradiol appears slowly in the urine, 40% after 5 days, as glucuronides and sulfates, with a minor amount unconjugated. Up to 20% of ethinyl estradiol may be excreted in the feces [14].

Exogenous estrogens

Estradiol

Because 17β-estradiol is the principal estrogen produced by the ovary during the reproductive years and during the perimenopausal transition, there is good reason to understand its pharmacokinetics for hormone replacement [8]. For one reason, estradiol is the principal intranuclear estrogen in the cell and is responsible for most biologic activity. Although estradiol may be ingested, it is often altered several times before finally binding to its nuclear receptor [15]. In order for oral estradiol to be absorbed by the gastric mucosa, it needs to be administered in a conjugated or micronized form. Estradiol valerate (widely used in Europe and approved by the Food and Drug Administration but unavailable in the United States) and micronized estradiol (Estrace) are two commonly used oral preparations with essentially identical pharmacokinetics. Estradiol is efficiently absorbed from the vaginal mucosa, such that whole tablets of the micronized hormone may be placed in the vagina with good absorption and serum levels [16]. Estradiol is also well absorbed through the skin in transdermal patches (Vivelle, Estraderm,

Table 1
Metabolic clearance rates for the major estrogens

Estrogen	MCR (L/d)
Estradiol	1350
Estrone	2210
Estriol	2100
2-Hydroxyestrone	39,125
2-Hydroxyestradiol	12,200
2-Methoxyestrone	2470
Estrone sulfate	146
Ethinyl estradiol	1070
Mestranol	1120

Abbreviations: MCR, metabolic clearance rate.
From Lobo RA, Cassidenti DL. Pharmacokinetics of oral 17β-estradiol. J Reprod Med 1992;37:77–84; with permission.

Climera). Estradiol creams, pellets, and implants are also quite effective methods of drug delivery, although availability is undependable in the United States.

Estradiol is quickly converted to estrone, which in turn is conjugated to estrone sulfate. Estrone sulfate serves as a large stable pool of estrogen in the circulation [17,18], but can be converted back to estrone or estradiol. When estrone reaches the cell membrane, it is converted to estradiol before reaching the nucleus, where it binds to a nuclear receptor to exert its action.

With oral administration of 1 mg of estradiol, serum levels of estradiol, estrone, and estrone sulfate increase rapidly to peak at 4 hours. Levels are fairly constant from 4 to 12 hours, after which they fall gradually. With chronic dosing, a steady-state level is reached within 2 to 4 weeks, after which time levels seen 24 hours after dosing are pretty representative of the levels throughout the day [19,20]. Levels of estrone glucuronide peak at 1 hour, than gradually fall to baseline.

Estrone sulfate piperazine (also known as estropipate) is quickly metabolized to estrone sulfate after oral administration. A dosage of 1.5 mg of piperazine estrone sulfate results in nearly superimposable levels of estradiol and estrone sulfate in the first 6 hours after dosing if compared with 2 mg of estradiol valerate (Table 2) [9].

Table 2
Expected mean serum levels of estradiol and estrone after oral dosing with the indicated estrogen

Dose (mg)	Estradiol (pg/mL)	Estrone (pg/mL)
Estrone sulfate, 0.625	34	125
Estrone sulfate, 1.25	42	220
Estrone sulfate, 2.5	126	356
Micronized estradiol, 1	35	190
Micronized estradiol, 2	63	190
Micronized estradiol, 2 (chronic)	122	330
Estradiol valerate, 1	50	160
Estradiol valerate, 2	60	300

Conjugated equine estrogens are slightly more potent by a factor of 1.4 to 3.5. Ethinyl estradiol has profound potency compared with the other preparations by several hundredfold (it is administered in microgram doses and not milligram doses). The SHBG response of ethinyl estradiol has been particularly useful in the treatment of hirsutism, because the binding capacity for testosterone and estradiol increases dramtically.

Table 3 shows the potency of four different types of orally administered estrogen based on ability to suppress follicle-stimulating hormone, serum levels of cortisol-binding globulin, SHBG, and serum angiotensinogen [21]. Piperazine estrone sulfate and micronized estradiol are nearly equipotent for all responses on a weight basis.

The most popular prescribed estrogen for menopausal replacement in the United States is Premarin, extracted from the urine of pregnant horses. It contains the classic estrogens already discussed but also the equilin estrogens, which are unsaturated on the B ring and are not native to humans. Conjugated equine estrogen (CEE) contains estrone sulfate 45%, equilin sulfate 25%, 17α-dihydroequilin sulfate 15%, 17β-dihydroequilin, and trace amounts of several other equilin compounds. These compounds are presumably produced by the fetoplacental unit of the pregnant mare. Estrone and equilin have very similar binding properties and metabolic fates, as do both estradiol and 17β-dihydroequilin. The equilins are potent estrogens capable of stimulating the endometrium to proliferate by mechanisms similar to the classic estrogens [22]. Equilin sulfate is reported to be 1.5 to 8 times more potent than estrone sulfate in stimulating hepatic production of SHBG, corticosteroid-binding globulin, and angiotensinogen [23]. 17β-Dihydroequilin has increased binding affinity to the estrogen receptor when compared with estradiol, although estrone binds more tightly than equilin [22]. The pharmacokinetics of equilin sulfate is similar to those of estrone sulfate. The biologic effects of CEE are primarily from estrone sulfate and equilin sulfate and their respective metabolites [22].

Vaginal estrogen

Vaginal administration of estrogen is well absorbed and can be accomplished with tablets, rings, creams, and suspensions. When estrogen is administered in

Table 3
Potency of four different types of orally administered estrogen

Estrogen preparation	Serum FSH	Serum CBG	Serum SHBG	Serum angiotensinogen
Piperazine estrone sulfate	1.1	1	1	1
Micronized estradiol	1.3	1.9	1	0.7
Conjugated estrogens	1.4	2.5	3.2	3.5
Ethinyl estradiol	80–200	1000	614	232

Abbreviations: CBG, corticoid-binding globulin; FSH, follicle-stimulator hormone; SHBG, sex hormone–binding globulin.

saline, the pharmacokinetics is highly similar to those of intramuscular administration [24]. Micronized estradiol is also well absorbed in tablet form [25]. When estrogen is delivered as a cream, absorption is attenuated and estrogen values are only one fourth of those expected after a similar dose is administered orally [25]. Only rings and creams are approved for clinical use. In pilot studies, vaginal rings containing 100, 200, and 400 mg of estradiol produced constant and sustainable serum levels of estradiol in the range of 40, 70, and 140 pg/mL, respectively [26]. The only vaginal ring for clinical use is Estring, however, which contains only 2 mg of estradiol and is suitable only for the relief of urogenital atrophy.

Vaginal administration of estradiol bypasses the intestinal-hepatic first-pass effect and results in bioactive estrogen and serum levels that exceed those after oral intake [27]. Vaginal administration of 0.5 mg of 17β-estradiol (micronized in saline) results in levels 10 times higher than those achieved with 2 mg of estradiol administered orally [28]. The vaginal absorption of estradiol results in serum levels 40 times higher than after oral dosing.

Vaginal administration of estradiol or CEE in cream form is most useful for the treatment of urogenital atrophy because absorption is relatively poor. One gram of Premarin vaginal cream contains 0.625 mg of CEE and results in serum levels of approximately 25 pg/mL of estradiol and 60 pg/mL of estrone [25]. This is less than one half of expected serum levels after oral ingestion and is similar to levels experienced in the very early follicular phase.

Progestagen compounds

Progesterone is a sex steroid produced in significant amounts only by the luteal phase ovary and the fetoplacental unit in the reproductive-age woman. It is produced by the adrenal gland in small amounts (less than 1 mg/d) but in large amounts in the postovulatory ovary (30 mg/d). Its function is implicit in its name, *pro*gestation, because it serves to provide the endometrial secretory characteristics necessary for embryonic implantation and sustenance of the pregnancy. Withdrawal of progesterone during the luteal phase or during pregnancy causes endometrial shedding and menstruation. Progesterone causes decidualization of the endometrium if it is estrogen primed and antagonizes the effects of estrogen in the endometrium if given with or before estrogen stimulation. Unopposed estrogen stimulation of the endometrium leads to endometrial hyperplasia [29]. The combination of estrogen and progestin, as in the oral contraceptive pill, produces a thin and eventually atrophic endometrium. Progestogen is necessary to prevent endometrial hyperplasia if estrogen is administered for hormone replacement therapy in the menopause.

Progesterone is the only natural progestagen with any significant biologic function. Progesterone is metabolized principally in the liver by the 5α-reductase pathway resulting in pregnanediol and pregnanetriol and conjugation with glucuronide. Pregnanediol glucuronide is found excreted in the urine. Progester-

one's precursors and metabolites do not have significant progestational activity. Progesterone circulates in the serum bound to cortisol-binding globulin, bound to albumin, or free. The metabolic clearance rate for progesterone is 2100 to 2500 L/d and is not significantly influenced by its protein binding [30].

There are many synthetic progestagens with potent effect. These are divided into two basic classes: those structurally related to progesterone and those structurally related to testosterone. The progesterone-like compounds include 17-hydroxyprogesterone acetate, medroxyprogesterone acetate, megestrol acetate, and cyproterone acetate. The testosterone-like compounds are divided into two groups: those related to norethindrone (norethindrone acetate, ethynodiol diacetate, norethynodrel, and norethindrone enanthate); and those related to levonorgestrel (desogestrel, norgestimate, and gestodene). The latter compounds related to levonorgestrel are often referred to as the *new generation* progestogens.

The norethindrone-related compounds listed previously all act as prodrugs, with norethindrone being the active compound, which binds to the progesterone receptor. Its binding affinity is 85% that of progesterone [31]. The prodrugs bind with affinities of less than 10% that of progesterone. The levonorgestrel compounds are a mixed group. Levonorgestrel and gestodene both bind with high affinity to the progesterone receptor [31,32]. Desogestrel binds only weakly, but acts as a prodrug, which is metabolized to 3-ketodesogestrel that has high affinity for the progesterone receptor [32]. The mechanism by which norgestimate exhibits its progesterone action is not well known. Norgestimate has less than 1% relative binding affinity as compared with progesterone, but it probably acts after being metabolized to levonorgestrel [33]. There is much variation in the literature regarding the relative affinity of the progestagen compounds for progesterone receptor. The variation comes from both the species from which progesterone receptor is derived from and differences in experimental technique [34]. Although norethindrone has less affinity for the progesterone receptor in some studies, it is many times more potent than progesterone and causes secretory changes in the endometrium.

Several studies have examined the biologic activity of various synthetic progestogens in the human endometrium [35,36]. After estrogen priming with CEE for at least 3 months, the effects of progestogen treatment after dilation and curettage were assessed by endometrial morphologic criteria and by quantitating cellular products, such as estrogen receptor, dehydrogenase enzymes, and DNA. The results show that if norethindrone is used as a standard, levonorgestrel is eight times more potent, whereas medroxyprogesterone acetate and progesterone have 9% and 0.2% of the activity of norethindrone, respectively.

A review of the human data concerning oral contraceptive pills has been done [37]. Different progestogen-containing oral contraceptive pills were compared for their effect on endometrial histology, delay of menses, and serum lipid effects. This study found that there is remarkable similarity of potency of the dose of various progestogens used in many of the formulations available in the United States. Norethindrone, norethindrone acetate, and ethynodiol diacetate are roughly equivalent in potency, whereas levonorgestrel is roughly 10 to 20 times

as potent. This potency difference is taken into account to a large degree by adjusting the content of progestogen in the formulation of the tablets. The serum half-life of the synthetic progestins (oral dosing) is similar and much larger than that of ingested micronized progesterone. Levonorgestrel has a serum half-life of near 13 hours, desogestrel has a half-life of 12 hours, and norethindrone a half-life of 8 hours (Table 4).

Progestogens: nonoral delivery systems

Crystalline progesterone is poorly absorbed orally, although micronized progesterone is well absorbed. This has allowed production of a commercial product that is a relatively new alternative to synthetic progestogens for hormone replacement therapy (Prometrium). Micronized progesterone administered at 200 mg daily for 12 days each month with oral CEE was very effective in preventing endometrial hyperplasia associated with unopposed estrogen replacement therapy [29]. After oral administration, peak levels or 8 to 20 ng/mL are reached in 2 to 8 hours after a 200-mg dose with much variation between subjects [38]. Because full decidual transformation of the endometrium cannot be achieved with oral progesterone, oral progesterone is not used for luteal support after in vitro fertilization [39].

Table 4
Summary of the pharmacokinetics parameters and serum-binding distribution of norethindrone, levonorgestrel, gestodene, and 3-ketodesogestrel

Parameter[a]	NET (1000 μg)	LNG (150 μg)	GSD (75 μg)	KDG (150 μg)
C_{max} (ng/mL)	15.7	3.4	3.8	2[b]
t_{max} (h)	1.2	1.4	1.7	1.6[b]
F (%)	64[c]	89		
$t_{1/2}$ β (h)	8[c]	13.2	10	12.6
CL (mL/h/kg)	355[c]	105	48	174
Vd (L/kg)	3.6[c]	1.9	0.7	3
Binding (%)				
SHBG	35.5	47.5	75.3	31.6
Albumin	60.8	50	24.1	65.9
Unbound	3.7	2.5	0.6	2.5

Abbreviations: GSD, gestodene; KDG, 3-ketodesogestrel; LNG, levonorgestrel; NET, norethindrone; SHBG, sex hormone–binding globulin.

(*From* Stanczyk FZ. Structural-function relationships, potency, and pharmacokinetics of progestogens. *In*: Labo RA, editor. Treatment of the postmenopausal women: basic and clinical aspects. New York: Raven Press; 1994. p. 69–89; with permission.

[a] Values for the maximum concentration (C_{max}) and time to reach C_{max} (t_{max}) were determined following oral dosing. The absolute bioavailability (F) was calculated after oral and intravenous dosing. The half-life of elimination ($t_{1/2}\beta$), clearance (CI), and volume of distribution (Vd) were determined after intravenous dosing.

[b] The C_{max} and t_{max} of 3-ketodesogestrel were determined following desogestrel administration.

[c] This value was determined after norethindrone acetate administration.

The efficiency of vaginal absorption of micronized progesterone is very good. Progesterone administered nonorally can duplicate the endometrial effects observed in a natural menstrual cycle, whether given intramuscularly or vaginally [40]. Vaginal or intramuscular progesterone results in more even serum levels compared with oral dosing because of avoidance of the first-pass effect. Although serum levels are higher after intramuscular dosing compared with vaginal dosing, endometrial levels are higher after vaginal dosing when compared with intramuscular or with the natural ovarian cycle [41]. After 7 days of intramuscular or vaginal progesterone, no differences between either treatment regimen or control groups were detected by histologic, ultrasonographic, or immunocytochemical receptor analyses [41].

A new delivery system for vaginal progesterone has recently been developed by progesterone is administered vaginally with a controlled-release gel, Crinone. This can limit the number of application to one per day while allowing relatively constant endometrial progesterone levels [39]. Recently studied were two groups of women on low-dose vaginal progesterone in a vaginal gel called Crinone 4% [40]. Continuous estrogen was used in all patients studied. Cyclical use of Crinone 4%, 10 consecutive days each month, was associated with predictable withdrawal bleeding in 91% of users with no evidence of endometrial hyperplasia. A second group of women using twice-weekly Crinone 4% and continuous estrogen were mostly amenorrheic (54 of 67 users) throughout 6 months of continued use. Vaginal delivery of progesterone allows high concentration of drug to the endometrium while allowing low levels of systemic delivery. If future studies reproduce the high rate of amenorrhea seen here, vaginal progesterone delivery systems could prove highly useful.

Another progestogen product with high local delivery of steroid to the endometrium is the levonorgestrel intrauterine device. The levonorgestrel intrauterine device is a T-shaped device with a polydimethylsiloxane collar attached to the vertical arm, which contains 46 mg of levonorgestrel, released at a rate of 20 μg/d. This low level of progestin exposure is just a little less than is released by Norplant, but endometrial levels of levonorgestrel are considerably higher. The levonorgestrel intrauterine device reliably produces endometrial atrophy, despite fluctuating serum estradiol levels that result from incomplete hypothalamic-pituitary-ovarian suppression. Local levonorgestrel produces decreased uterine blood flow as demonstrated by a significant increase in the uterine artery pulsatility index [42]. The levonorgestrel intrauterine device has not eliminated breakthrough bleeding despite the decreased menstrual flow observed by most users. After 90 days, however, amenorrhea or light regular menses is realized by most users with a near 90% reduction of menstrual blood loss.

The pharmacology of oral contraception is covered in detail elsewhere. Of interest to note here is the similarity in synthetic steroid metabolism and effect after either oral or vaginal administration. When a standard-dose oral contraceptive pill containing ethinyl estradiol and levonorgestrel is administered vaginally, serum concentrations of levonorgestrel and SHBG are almost indistinguishable after the first 24 hours [43]. In a small study of vaginal administration of a 30 mg

ethinyl estradiol and 0.15 mg levonorgestrel pill, it was concluded that vaginal administration suppresses ovulation well with minimal side effects [44].

Summary

Estradiol and progesterone are produced in abundance by the ovary of the reproductive-age female (and by the placenta in pregnancy). Serum levels of both hormones are very low in the postmenopause, and indistinguishable from women who have undergone castration. Postmenopausal women have higher levels of aromatase in skin and adipose and convert androstenedione to estrone more effectively than younger women.

Estradiol is well absorbed orally, but undergoes extensive first-pass effect resulting in production of the less potent metabolites estrone and estrone sulfate. Ethinyl estradiol is well absorbed, potent, and has more pronounced effects in the production of important hepatic proteins.

Progesterone is absorbed orally only if ingested in a micronized form, has a relatively short serum half-life, and is metabolized to products with little biologic activity. The synthetic progestogens are abundant in number; potent in effect; and well absorbed orally, vaginally, and transdermally.

New formulations of estrogens and progestogens and new delivery systems promise to provide gynecologists and patients with a long list of potential solutions to contraceptive needs and alternatives for hormone replacement therapies.

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The role of reproductive hormones in maintaining cognition

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It is an exciting challenge to be a practitioner in women's health care. Although traditionally held benefits of hormone replacement therapy (HRT) are being challenged, compelling evidence of previously unappreciated benefits is emerging. This phenomenon is most dramatic in the study of cognition. The impact of sex steroids, most notably estrogen, on the central nervous system (CNS) is profound and diverse. Currently, there are over 300 journals published annually that are devoted to the study of neuroscience. Moreover, it is a rare occurrence for one of these journals not to address this subject.

This article summarizes the current data describing the relationship between reproductive hormones and cognition on women during the late reproductive years and the perimenopause. The wealth of data on the relationship between hormones and other brain functions like mood, behavior, coordination, sexuality, or sleep are not reviewed. A review of hormonal therapy in patients with established neurodegenerative diseases like Alzheimer's disease or Parkinson's disease is also not provided. The interested reader is encouraged, however, to pursue these subjects and it is hoped those issues can be addressed in future publications.

Cognition: the often overlooked symptom of the menopausal syndrome

Cognition is a term describing a variety of brain functions including memory, learning, language, attentiveness, reasoning, and motor speed. The Study of Women's Health Across the Nation recently confirmed that memory problems rank among the most common complaints of women experiencing menopause in the United States regardless of their racial background. As a result of techniques developed during the last decade, clinicians are beginning to understand the association between hypoestrogenism and memory problems. The development of a vast knowledge base has enabled clinicians to generate physiologic

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hypotheses that are being tested experimentally. Most of the data strongly suggest that HRT promotes brain functioning in women as they develop and protects brain functioning as they age. This information has become even more important as the dramatic growth of the post–reproductive-aged population is seen.

An urgent call to action

Women in the United States can anticipate a life expectancy of over 82 years. Although many argue that menopause is natural and not worthy of treatment, a glimpse at the life expectancy curve for women through prehistory demonstrates a dramatic increase in life expectancy (Fig. 1). The increase in lifespan has resulted in women spending a third of their years in the phase of their life following ovarian failure. With the increase in the number of people living into their eighth decade there has been a proportional increase in risk of developing dementia. It is noteworthy that Alzheimer's dementia, by far the most common of all dementing illnesses, is 3.1 times more common in women at any age than men. In the United States, it was recently reported that a woman's lifetime risk of developing Alzheimer's dementia is about one in three. In fact, if a woman lives to age 90, her risk is approximated to be as high as 50% [1]. The population of menopausal women in the United States is expected to increase from about 40 million to nearly 50 million within this decade alone [2]. It is not surprising that although the number of US citizens with dementia has already exceeded 4 million, this number is expected to swell to around 16 million within the next 50 years. In fact, the Institute of Medicine lists brain-related disorders as the largest single cause of disability. It is important to note that this is a quality-of-life issue. Alzheimer's disease does not generally kill its victims; instead, it robs them of their identity, their personality, and ultimately their ability to administer self-care.

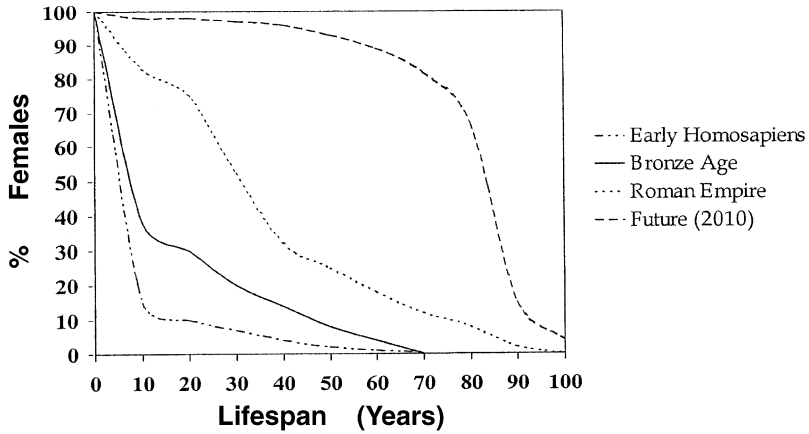

Fig. 1. Life expectancy of women.

The genderification of the brain

It has long been recognized that there are significant cognitive and behavioral differences between men and women. With the twentieth century came microscopic study of human anatomy that subsequently revealed details in brain structure. The evolution of modern psychologic testing demonstrated that despite differences in brain size there is no overall difference in cognitive ability between men and women and only limited difference in macroscopic structure (Table 1). Through the maturation of the fields of hormone research and neuroscience clinicians are now beginning accurately to measure the differences between the male and female brain. Currently, studies are differentiating the effects of hormones on brain development (organizational effects) from those involved in brain functioning (activational effects). It is now being recognized that the adult brain retains enough plasticity that there can be some overlap of organizational effects that can reflect dramatic changes in circulating hormone levels. This has been demonstrated most convincingly in transgender adults undergoing profound hormonal changes [3]. Because this article is devoted to perimenopausal women, it focuses on the activational effects.

When groups are studied, women tend to perform better than men on verbal memory tasks, whereas men tend to outperform women on spatial tasks and tests of abstract reasoning. Even within the normal menstrual cycle, cognitive testing has revealed that women tend to do better on spatial and abstract reasoning skills during menstruation (when estrogen levels are low), but better on verbal and fine motor tasks at midcycle (when estrogen levels peak) [4,5]. It must be pointed out that these findings, although demonstrated consistently, are only reflected when large groups are studied because of the tremendous individual variation among humans.

The complex interrelatedness of the sex hormones in the CNS

The effects of estrogens on the CNS have been the most widely studied of all of the steroid hormones. As a result of its profound impact on the brain, estrogen is

Table 1
Confirmed differences between the male and female brain in humans

Men	Women
Larger total brain mass	Smaller brain ventricles
Higher neuronal density and number	Higher number of neuronal branches
Larger planum temporale and left anterior fissure	Larger, more bulbous posterior corpus callosum
Larger medial preoptic nucleus	Larger ventromedial nucleus
* Stronger androgen receptor binding in mamillary body complex	* Stronger estrogen receptor binding of dorsolateral supraoptic nucleus

* Current data suggest this binding affinity may reflect a function of circulating hormone levels rather than a true gender difference.

Table 2
Effects of estrogen on the central nervous system

Nongenomic
Rapid actions
Promote cerebral blood flow
Augment signal conduction
Modulation of certain receptors
Protect from oxidative damage
Intermediate action
Promote glucose uptake
Promote neuronal metabolism (ie, cAMP)
Modulation of inflammatory response
Genomic
Promote neuronal growth and differentiation
Guide cytoarchitectural structure of the brain
Promote synaptic connections in the hippocampus
Increase production of certain neurotransmitters (ie, acetylcholine)
Increase concentration of neurotransmitters (ie, promote degradation of monoamine oxidase)
Create cytoarchitectural changes of neurons (ie, neuronal spine formation and receptor production)

described within the field of neuroscience as a pleiotropic hormone. Within the brain, estrogen is used in a variety of ways (Table 2). It is often synthesized from testosterone within the brain through the presence of aromatase enzymes necessary to facilitate this conversion. The brain can also make progesterone and dehydroepiandrosterone (DHEA). The brain has emerged as the most complex endocrine gland, yet described with the pituitary gland acting as its chemical messenger rather than the ''master gland'' it was previously considered to be.

What is memory and how is it stored?

Before describing the effects of hormones on memory and cognition, current theory on how the brain stores and recalls information is reviewed. Data are believed to be stored as patterns of neuronal connections known as *networks*. Information is categorized as either declarative (explicit) or nondeclarative (implicit) memory. Declarative memory includes facts, figures, and specific events. Nondeclarative memory is defined as procedures and functions that are performed so frequently that they are almost automatic, such as walking or driving. Nondeclarative memory is more resistant to the process of forgetting.

Information is processed through multiple stages as it is stored. For example, working memory is useful only for the briefest of times before it is lost. The average person can store about seven bits of information in this system. It is not coincidental that so many items that require short-term memory storage are limited to seven or less. Telephone numbers are a typical example cited.

For working memory to be retained, it must be converted to short-term memory, a process believed to occur in the hippocampus. Information in the short-term system can be recalled for hours to days. To save information for the

remote future, it has to be processed into long-term memory. Current research is attempting to define exactly how this process occurs but it involves a complex relationship between sleep, neuronal branching, and neuronal membrane changes referred to as *long-term potentiation*.

The networks of memories exist in the layers that make up the cerebral cortex. There is a redundancy that exists in the paths to trigger the recall process for these networks. A variety of stimuli may provide alternate routes to activating these networks and result in the process of remembering. A popular metaphor for this process is one's "train of thought." This simplified review of memory theory reveals the complexity of this process called cognition. It serves as an appropriate transition into examining the impact of hormones on cognition.

Sex hormones and the CNS

Before describing hormonal effects of each steroid hormone's relative contribution to the cognitive process, it is worth noting the correlation between circulating levels and physiologic effects. The adrenal androgens (DHEA and DHEAS) are by far the most abundantly produced of the sex hormones. They are also the only ones lacking an identifiable receptor at the cellular level. Additionally, there has been no specific effect identified for this hormone within the brain. As the focus is shifted from progesterone to testosterone and from testosterone to estrogen, a progressive decline is found in mean circulating levels and increasingly complex and lengthy physiologic effects. For example, the presumptive number of actions identified to be related to progesterone in the female body is estimated to be between 50 and 100, whereas that of testosterone is estimated to be around 200. The growing list of physiologic effects of estrogens, however, has already exceeded 400. It becomes reasonable when considering steroid metabolism that more profound effects are observable from estrogen deprivation than from loss of testosterone, progesterone, or DHEA.

Traditionally, hormones were believed to act only through mechanisms that involved binding to the intracellular hormone receptors. These hormone-receptor complexes then modified cell functioning most commonly through the cell's DNA. Using this model, cellular changes are limited to cells that possess the appropriate hormone receptors. Additionally, a considerable time delay is required to facilitate this process. Many of estrogen's effects occur far too fast and in the absence of estrogen receptor (ER)$-\alpha$ or ER-β to fulfill these requirements. These rapid effects have come to be known as the *nongenomic mechanisms*.

DHEA: neurosteroid or precursor?

Dehydroepiandrosterone has become a popular product of the complementary-alternative medical community. It is directly available to consumers through health food stores and Internet sales. Because DHEA levels steadily decline with advancing age, it has been proposed that supplementation with DHEA might

slow the aging process and prevent such degenerative diseases as Alzheimer's disease. As intriguing and exciting as this sounds, human studies have not convincingly supported this theory.

Circulating DHEA, which is considered to be a week androgen, is primarily of adrenal origin. Production begins in childhood and peaks during the third decade. Then DHEA levels gradually decline until only a small fraction of the peak serum level is found during the menopausal years. Without any direct activity at the cellular level, or any hormone receptors for DHEA, its greatest function is likely to serve as a precursor to testosterone, its closest related hormone. High levels of DHEA have been found in the developing brain of rodents [6].

Human studies have also confirmed that DHEA is produced within the brain. Relatively high levels have been isolated from spinal fluid and brain tissue in patients who were status postbilateral adrenalectomy. Both astrocytes and neurons have the enzymes necessary to produce DHEA [7]. In fact, neuron studies suggest DHEA (added to cell culture media or in vivo) promotes growth of nerve cell fibers needed to form electrical connections in the brain [8].

It is feasible that DHEA may be involved in early brain development, as suggested by Compagnone et al [9] who believe it plays a role in establishing connections from the thalamus to regions of the rodent cerebral cortex. It remains to be established whether this occurs in primates. Unlike humans, rodents have very low DHEA levels making it a poor model for comparative studies.

One study on a small number of depressed patients noted improvement in depression rating scores during oral DHEA supplementation of 30 to 90 mg/d as compared with placebo [10]. Arlt et al [11] found that 50 mg of oral DHEA supplementation resulted in an improvement in self-rated depression scores, anxiety, sexual interest, and satisfaction with sex life in women with adrenal insufficiency. DHEA had no influence on cognition in either study. It is not clear if DHEA had a direct effect or if it simply served as a precursor for subsequent conversion to other hormones in these patients because the androgen levels went up during treatment. An in vitro study found that decreased DHEA levels may contribute significantly to increased vulnerability of the neurons to stress and aging [12]. Several researchers have tried to find a correlation between DHEA levels and cognitive ability, but no consistent association has been found. The difficulty with the existing human studies is their small numbers, varied end point measurements, and brief treatment times. To summarize the data on DHEA's effect on cognition, a recent Cochrane Review of the current DHEA literature found no supportive evidence for an improvement in memory or other cognitive functions following administration of DHEA in normal older individuals [13]. Clearly, there is a need for larger studies with more precise experimental designs to clarify what if any association exists between DHEA and aging. It is possible that falling DHEA levels associated with aging merely reflect a reduced production of sex hormones and their precursors as women enter the postreproductive years.

Dehydroepiandrosterone is being marketed to consumers seeking alternative therapies as the "super hormone," "the fountain of youth," and the "mother of all hormones" with claims of better memory; longer life; improved libido; weight

loss; improved sense of well-being; improved immune response; and prevention of such diseases as depression, diabetes, heart disease, Alzheimer's disease, and AIDS-related complications. Despite these miracle claims for DHEA, the truth is there is not enough evidence to support any claim of significant benefits from DHEA supplementation with the possible exception being patients with a true deficiency syndrome [11]. Relatively few studies have been done and little is known of any direct effect of serum DHEA on the adult brain. DHEA supplementation can increase androgen levels and any benefit to mood may be attributable to an increase in testosterone. Because there is a potential for irreversible androgenic side effects, caution must be used if supplementation is started.

Progesterone and the brain

There are progesterone receptors in several regions of the brain, yet only limited information exists as to its functions in the CNS (Fig. 2). It has long been recognized that the addition of progesterone to a hormone replacement regimen causes many women to have additional side effects including sedation, irritability, and depression [14]. Many studies have shown progestins to have a deleterious affect on mood and sense of well-being. Sherwin [15] compared the effects of 5 mg medroxyprogesterone acetate with 0.625 or 1.25 mg conjugated equine estrogens and found women on estrogen alone reported enhanced mood, whereas women on progesterone reported a negative mood effect and greater frequency of psychologic symptoms.

The side effects of progesterone and progestins have been shown to be dependent on dose and route of administration. Following oral administration of 1200 mg progesterone, women were found to have side effects proportional to the level of metabolites found in the bloodstream [16]. There was significant variability in metabolite levels among patients in the study.

One of the active metabolites of progesterone is pregnenolone, which binds the GABA$-\alpha$ receptor. The GABA$-\alpha$ receptor has known anxiolytic effects. In fact, pregnenolone can bind the receptor more tightly than alcohol, benzodiazepines, or barbiturates [17]. If progesterone is administered orally it seems to produce greater side effects and is noted to have higher serum levels of the active metabolites than the same dose administered vaginally [18,19].

It is not clear what effect progesterone has on cognition. Wooley and McEwen [20] measured neuronal dendrite density in the hippocampus of female rats during phases of the menstrual cycle. It was noted that the dendrite density decreased when estrogen levels dropped (presumably making it a progesterone-dominant phase). These sorts of studies force one to ask if adding a progestin to an estrogen-replacement regimen may counteract the benefit of estrogens on the brain. A study of 837 elderly Japanese women (either on no hormones, estrogen replacement therapy [ERT], or HRT over 2 years) found an increase in cognitive scores of women on estrogen alone, but a decrease in cognitive performance scores of the women on estrogen and progestin [21]. Berman [22] studied young

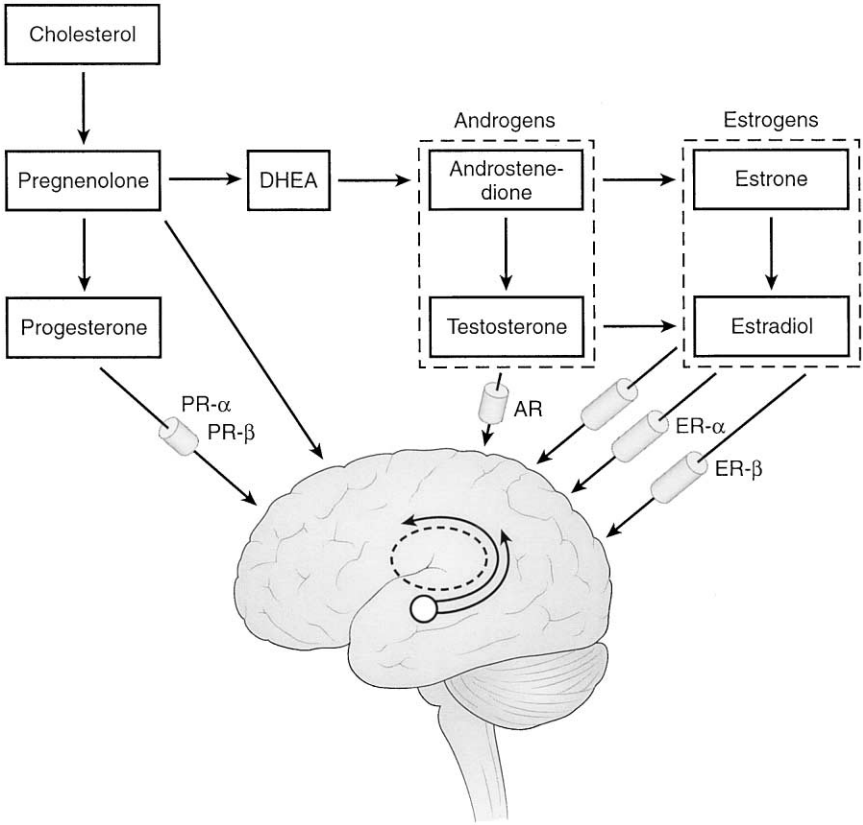

Fig. 2. There are various described mechanisms for how sex hormones influence the brain. They can be enzymatically converted or act through their receptors. Although there are two known progesterone receptors, it is not known if they have different effects or distribution in the human brain. For that reason, they are presented with only one common receptor. Estrogens and pregnenolone are known to have receptor-independent effects on the brain. Emerging data have demonstrated that there is a differential effect on the brain between estrogen receptor−α and estrogen receptor−β.

women being treated with leuprolide (pharmacologically causing postmenopausal hormone levels). Positron emission tomography scans were done while patients performed cognitive testing. Regional cerebral blood flow was measured with positron emission tomography after addition of estrogen or progesterone. Differential areas of increased blood flow were observed depending on which hormone was added, demonstrating in this study that estrogen and progesterone do have different physiologic effects on the brain. This study, however, failed to demonstrate any cognitive differences between the two regimens.

Although no firm conclusions can be made, it is possible that progesterone may cause some of the beneficial effects of estrogen on cognition and mood to diminish. Progestins have a dose-dependent side effect profile and it is reasonable to suspect that low doses have a minimal effect. Progestins are a necessary adjunct to estrogen

in women who have an intact uterus, so further study is needed to determine which progestins have the best (or least detrimental) effects on mood and cognition.

Testosterone: direct effect or targeted delivery of estrogen?

It is beyond the scope of this article to describe the effects of testosterone on sexuality and behavior. It is worth noting, however, that recent studies with male and female knock-out mice suggest that gender-specific behaviors are markedly diminished in the absence of ER-α [23]. Similar studies suggested that many of the typical behaviors that are more common in males, for example territorial behavior and aggression, were also diminished in the absence of ER-β. In females that were lacking ER-β, there was also atypical sexual behavior [24]. If confirmed in humans, these findings will provide further evidence that testosterone serves primarily to target cells within the CNS that manifest their actions through conversion to estradiol-17β.

Exactly how testosterone may impact cognition is more difficult to determine. It has long been observed that when large groups of men and women are compared the men tend to do better on tests for nonverbal skills and spatial-visual categories of intelligence. The women tend to excel on tests of verbal memory and processing speed. It has also been noted by several investigators that some women note fluctuations on various cognitive functions that reflect the hormonal changes of the menstrual cycle. For example, female performance tends to be most similar to male during the follicular phase of the menstrual cycles [25]. This is also the time of peak estrogen and testosterone levels and the lowest progesterone levels.

Miller et al [26] demonstrated that the cyclic fluctuations in free testosterone and estrogen levels can be stabilized with oral contraceptives. This intervention was an attempt to isolate specific hormonal effects for cognitive studies. The most consistent finding in the literature has been a mild but significant decrease in cognitive abilities during the phase when hormone levels are at their lowest. Of course, this finding has important implications on aging and ovarian senescence.

When evaluating the effects of androgen administration studies, one must consider that the highest concentration of androgen receptors in the brain is in the same regions that direct behavior, not cognition (hypothalamus, preoptic area, and substantia nigra). These same areas correspond with an approximately sevenfold increase in aromatase activity. This enzyme, used to convert testosterone to estrogen, is more active in these corresponding areas than anywhere else within the brain. With the clinical use of aromatase inhibitors to treat breast cancers, it may become more apparent what the isolated effects of androgen administration are in the absence of their conversion to estrogens.

Testosterone supplementation has been demonstrated to improve working memory in men but not in women [27]. It is worth noting that testosterone administration also impacts the bioactive hormone levels indirectly through inhibitory effects on sex hormone–binding globulin. Several studies have demonstrated a correlation between free estradiol levels and cognition [28].

Estrogen and CNS: genomic and nongenomic effects

Estrogen has so very many effects on the CNS, an attempt to summarize them could easily fill an entire article on its own. Not having that luxury, some of the effects that are believed to have the most profound impact on cognition are now summarized. Some of these studies have been performed in tissue cultures, others in animals, and still others in humans. When viewed collectively, however, it is very obvious that estrogen has beneficial effects on the CNS at multiple levels and it is noteworthy that as yet there are no adverse effects in the CNS that have been described.

To begin with, a review of some of the key nongenomic mechanisms by which estrogen can impact cognition follows. For example, estradiol-17β has been demonstrated to increase spontaneous firing of some neurons [29] and decrease the firing of others [30] within seconds of exposure. These effects are most likely to occur through direct effects on the neuronal membrane. The steroid hormones have also demonstrated the ability to act through various second messengers. For instance, estrogen, testosterone, and progesterone have the ability to affect cAMP levels and membrane potential through inhibition of GTPase activity [31]. Additionally, various estrogens, and to a lesser degree progestins and androgens, have demonstrated the ability to effect intracellular calcium concentration through a variety of mechanisms [32] and in ways that are gender specific [33]. When considering the speed with which various brain functions are carried out, these mechanisms provide some possible explanations for estrogen's observed increase on processing speed [34,35].

Estrogen also has various neuroprotective effects, some of which are manifest through nongenomic pathways. These include the ability of the "A" rings' hydroxyl group to act as a free radical scavenger, an antioxidant. In fact, various studies have demonstrated the varying potency of estradiol-17β, estradiol-17α, estrone, and even estriol to minimize effectively the damage of oxidizing challenges [36,37]. Of particular importance in understanding estrogen's protective effects against various neurodegenerative diseases are the genomic and nongenomic means by which various toxic substances like β-amyloid and glutamate damage can be minimized [38–40].

Additional mechanisms by which estrogen seems to manifest nongenomic benefits on the CNS involve the delivery and metabolism of glucose. For example, estrogen augments brain blood flow through various vasodilatory mechanisms [41]. Estrogen also seems to modulate the vascular system directly through the CNS control of vascular tone [42] and on blood pressure and indirectly by acting as a modulator of the stress response. [43]. Blood flow is vital for normal brain functioning because of the brain's limited ability to function anaerobically. The human brain, which is typically around 3% of the average human's body weight, receives an estimated 20% of the resting cardiac output.

Several studies have demonstrated that not only do women typically have a higher cerebral flow rate than age-matched men performing the same function, but that there is a reduction in brain blood flow associated with menopause [44].

Additionally, more recent studies have correlated severity of hot flushes (vasoactive episodes) and blood flow distribution [45,46]. This becomes particularly important when one realizes that there may be a correlation between these blood flow changes and subsequent development of Alzheimer's disease [47].

Estrogen also has a direct impact on brain activation. This was documented through measurements of metabolism in regions of the brain during cognitive testing [48]. Dietrich [49] recently demonstrated that estrogen has acute effects within physiologic ranges common to the menstrual cycle; specifically, an enhanced perfusion during cognitive tasks performed during the high estrogen phase of the cycle was found. Another neuroimaging study demonstrated that postmenopausal women who are estrogen depleted have declining glucose metabolism patterns approaching those of patients with diagnosed Alzheimer's disease [50]. Its worth noting that this and other studies have demonstrated that age-matched women on estrogen replacement regimens have brain activation patterns that are not statistically different from women still experiencing menstrual cycles.

Finally, a new technique is providing information on neurotransmitter metabolism in vivo. MR spectroscopy, a noninvasive technique, analyzes regionalized signals of specified metabolites to quantify substances in targeted brain regions. Using this technique, it has been demonstrated that women on ERT have signals consistent with neuronal membrane stabilization, whereas those of estrogen-depleted women suggest neuron membrane catabolism [51]. Additionally, the geographic correlation demonstrates that the temporal and parietal lobe areas are most unstable in the estrogen-deficient patient, a finding that is also true of patients with Alzheimer's dementia. Other studies using similar neuroimaging techniques have shown that women on ERT and HRT have comparable signals for acetylcholine [52], dopamine [53], and serotonin [54] with women who are still cycling. These data support the in vitro studies demonstrating that estrogen has effects on neurotransmitter metabolism, acting to promote production of the neurotransmitters and the production of their receptors.

Estrogen effects how neurons differentiate. It effects how they are nourished. It then augments neuronal metabolism. Through these actions, estrogen augments brain activity and sensitivity to stimuli. It impacts communication between neurons and ultimately regulates the response and susceptibility to injury. Although the brain can function in the presence of very low estrogen levels, it is clearly less than an optimal condition for peak performance.

The differential effects of various estrogens on the CNS

Overall, estrogen seems to be the dominant steroid hormone impacting the brain. It is difficult, if not impossible, however, to make isolated conclusions about the effects of HRT. In humans, cognition is difficult to isolate and more difficult to measure. It is important to interpret studies in terms of which preparation is used and which outcome is measured. Generalizations are often

inaccurate. Different estrogens have different potency on the mechanisms described previously. ERT has a more profound impact when initiated in young women than older women who have been deficient for many years. This finding was demonstrated in a prospective, cross-over study of randomly assigned oopherectomized young women given either placebo or ERT [35]. In that study they measured a marked improvement in both short-term and long-term memory. Similar studies performed on older healthy menopausal women, however, demonstrate improvements more limited to specific categories of cognition including immediate recall and delayed recall, but the benefits were more subtle or even negligible in visuospatial memory [55–57].

When considering different realms of cognition, there are trends that emerge. Verbal memory improvement is the most consistent finding associated with ERT. Some studies have demonstrated preservation of visual memory when measured longitudinally [58]. Short-term memory effects are another consistent finding from various studies. This finding makes sense when considered with current receptor studies. The hippocampus, an important region for processing declarative memory, has an abundance of ERs [59,60]. These investigations may also provide the key to understanding the relative potency of various estrogens when considered in reference with the distribution of ER-α and ER-β.

A recent review and meta-analysis conducted by the US Preventive Services Task Force found that improvements in cognition were most dramatic in symptomatic women [61]. Their search revealed over 500 published abstracts, 50 of which have primary data available for analysis. Although results could not be combined to perform a conventional meta-analysis, the most consistent findings were improvements on verbal recall and vigilance followed by mental tracking, complex reasoning, and processing speed. There were much less data available on progestins but there was a trend toward diminished improvements with combination therapy. All findings were subtler in asymptomatic women.

There also needs to be consideration of the use of selective estrogen receptor modifiers. Studies are showing that tamoxifen has adverse effects on cognition that seem to be most dramatic in symptomatic women [62]. There has also been a correlation noted between duration of use and severity of cognitive problem. Recent results from the MORE trial demonstrated that raloxifene, another selective estrogen receptor modifier, apparently had a more neutral effect over the course of 3 years [63]. It is worth noting that there was a high dropout rate in that trial. If the patients dropped out of the study because of symptoms, this could have been an impact on the validity of the overall conclusion of a neutral effect.

Finally, studies on phytoestrogens are also providing some challenging data for interpretation. These plant hormones may affect cognition when consumed by humans. Two observational studies suggest there may be cause for some concern. The Honolulu-Asia Aging Study demonstrated an association between low cognitive test scores and high tofu consumption in a group of men living in Hawaii [64]. The Kame Study followed over 800 Japanese-American women living in the Puget Sound region of Seattle. In this population, estrogen use

demonstrated a protection from cognitive decline but the benefit was diminished in high tofu consumers [65]. Further study is warranted before conclusions are drawn. Soy phytoestrogens do bind preferentially to ER-β and only bind very weakly to ER-α [66]. Data from studies done on receptor knock-out mice suggest that ER-α is crucial to convey the genomic protection provided by estrogen to the CNS [67]. Other studies performed on oopherectomized rats, however, demonstrated improvements in working memory needed to complete an arm maze test when the rats were given phytoestrogens [68]. It seems premature either to caution or promote phytoestrogens to women inquiring about cognitive changes associated with menopause.

Circulating hormone levels and brain aging

Several studies have demonstrated an association between higher circulating hormone levels and cognitive performance in aging populations of women. It remains to be determined whether this observation is best correlated with testosterone level [69], free estrogen level [28], or both [70]. There is agreement that low sex steroid hormone levels are associated with a decline in cognitive performance. A confounding factor is the impact of the sex hormone levels on the physiologic stress response.

HRT and dementia

As difficult as it is to study hormonal effects on cognition, it is even more difficult to study the relationship of HRT and brain aging. Chronologically, dementia begins manifesting its effects about 12 to 15 years after the onset of menopause. Obviously, by this time in a patient's course it is very difficult to obtain accurate historical data about their menopausal symptoms and strategies for coping. Most of the studies that have been published are the result of observational studies or cohort studies. Even with these limitations, however, the information provides support for the use of estrogen to minimize the neurodegenerative diseases.

It is worthwhile to cite the recent meta-analysis performed by the US Preventive Services Task Force [61]. This study summarized that despite the limitation that conclusive statements could not be made about dose, duration, preparation, or progestins, they observed a statistically significant reduction in dementia in women with a history of estrogen use in menopause (Fig. 3). Other studies have suggested a possible reduction in rate of Parkinson's disease to dementia. The risk reduction estimates vary between 20% and 80%. Even with the most conservative estimates, estrogens top the list of interventions that seem to minimize the risk of neural aging.

The ideal studies to investigate these outcomes will be prospective, randomized, placebo-controlled trials. The Women's Health Initiative Memory Study

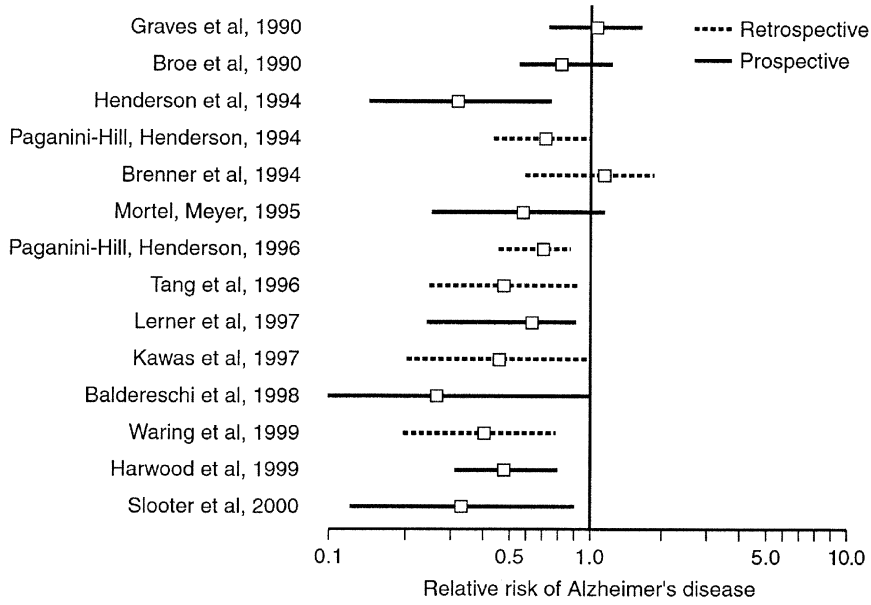

Fig. 3. Relative risk of Alzheimer's disease in estrogen replacement therapy users. (*Data from* Greene RA. Advanced reproductive endocrinology services. Redding Medical Center; 2002.)

[71] will provide further information to assist in advising patients. At this time, however, the data presented here and that which are emerging on a monthly basis should provide even the most cynical critic with the confidence to discuss estrogen and optimization of cognitive performance in aging women.

Summary

This article briefly reviews the impact of hormones on cognition. Estrogen has the most profound impact on brain functioning. Testosterone also seems to have significant brain-related benefits, whereas progesterone seems to have minor or possibly even adverse effects. As the field of neuroscience progresses, more definitive conclusions will follow. As the focus is shifted, however, from extending life to improving the quality of life, the existing data are very compelling.

The brain is a target for the sex steroid hormones. Clearly, this is an exciting and dynamic area for further study. Although skeptics may believe that more definitive proof is necessary before recommending hormone replacement for their patients to preserve their cognitive health, it seems prudent to discuss the evidence available to empower the patient further to guide their own treatment options and validate their symptoms. For those who still subscribe to the menopause-is-natural philosophy this question is posed, "why does the brain naturally have sex hormone receptors if they are not necessary?"

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Gynecologic problems of the perimenopause: evaluation and treatment

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Clinicians today appreciate that the perimenopause is a distinct entity from menopause, representing a transition period before the complete cessation of menses. In terms of symptomatology, the perimenopause may be even more important than either early or late postmenopause. Major gynecologic problems seen during the perimenopause include abnormal uterine bleeding and vasomotor disturbances. Other common gynecologic issues relevant to perimenopausal women include vaginal mucosal atrophy and sexual dysfunction. This article focuses on the evaluation and treatment of these problems.

Abnormal uterine bleeding

Changes in both menstrual flow and frequency represent the hallmark of the perimenopause. In one population-based sample of 380 women, 23% reported a change in menstrual flow only, 9% reported a change of frequency only, 28% reported a change in both frequency and flow, and 13% had not had a menstrual period for at least 3 months [1]. A chart review of 500 perimenopausal patients found that alterations in menstrual flow fit one of three patterns: (1) oligomenorrhea or hypomenorrhea (70%); (2) menorrhagia, metrorrhagia, and hypermenorrhea (18%); and (3) sudden amenorrhea (12%) [2].

Among perimenopausal women, abnormal uterine bleeding accounts for more than two thirds of office visits to the gynecologist [3]. Although changes in menstrual patterns and flow are considered a normal part of this transition, heavier-than-usual bleeding, prolonged bleeding, menstrual periods occurring more often than every 3 weeks, bleeding or spotting between menses, or bleeding after sexual intercourse are abnormal and require investigation [2,4].

A number of benign and malignant diseases of the reproductive tract, anovulation, and systemic diseases may cause abnormal uterine bleeding in a

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Table 1
Possible causes of abnormal uterine bleeding in perimenopausal women

Anovulation (dysfunctional uterine bleeding)
Benign reproductive tract conditions
Pregnancy
Leiomyomata uteri
Endometrial or endocervical polyps
Adenomyosis
Endometritis
Pelvic inflammatory disease; vaginal or cervical infection
Endometrial neoplasia
Endometrial hyperplasia without atypia
Endometrial hyperplasia with atypia
Endometrial adenocarcinoma
Systemic diseases
Coagulation disorders (thrombocytopenia, von Willebrand's disease, and leukemia)
Hypothyroidism
Liver disease
Iatrogenic causes
Hormone therapy
Contraceptive devices or injections

perimenopausal woman (Table 1) [4–6]. Clinicians must not overlook the possibility of pregnancy, because although fertility declines with age the potential for ovulation remains [7–9].

Abnormal uterine bleeding is the most common symptom of endometrial neoplasia [10]. Although endometrial neoplasia is uncommon among premenopausal women [11], the rate begins to increase sharply at age 45 [12,13]. In one study, 19% of perimenopausal patients with bleeding patterns other than amenorrhea or oligomenorrhea-hypomenorrhea had premalignant and malignant findings [2]. Independent factors associated with an increased risk of endometrial neoplasia

Table 2
Risk factors for endometrial neoplasia* in premenopausal women aged 17 to 50 with abnormal uterine bleeding

Risk Factor	Odds Ratio† (95% Confidence Interval)	P-Value
Age $\geq$ 45 y	3.1 (1.5–6.1)	.0016
Weight $\geq$90 kg	5.5 (2.9–10.6)	<.0001
History of infertility	3.6 (1.3–9.9)	.0127
Family history of colon cancer	5 (1.3–19.1)	.0182
Nulliparity	2.8 (1.1–7.2)	.0267
Family history of endometrial cancer	NS	NS

Abbreviations: NS, not significant.

Adapted from Farquhar CM, Lethaby MA, Sowter M, Verry J, Baranyai J. An evaluation of risk factors for endometrial hyperplasia in premenopausal women with abnormal menstrual bleeding. Am J Obstet Gynecol 1999;181;525–9; with permission.

* Endometrial hyperplasia or carcinoma.

† Multivariate analyses.

in premenopausal women with abnormal uterine bleeding include age 45 years and older, low parity, and obesity (Table 2) [10,11]. Because clinical models are only moderately effective in predicting endometrial neoplasia in women with abnormal perimenopausal bleeding, endometrial assessment is warranted in this setting [4,10,11,14,15].

Evaluation of abnormal uterine bleeding

A history with special emphasis on the clinical features of menstrual flow and restriction of daily activities, intermenstrual bleeding, contraceptive use, medications, and systemic diseases should be obtained in perimenopausal women presenting with abnormal uterine bleeding. A pelvic examination should also be performed. Pregnancy testing, serum levels of prolactin, thyroid-stimulating hormone, a complete blood count, and coagulation tests should be ordered selectively. Assessing gonadotropin levels is not useful in this setting [1]; perimenopause represents a clinical diagnosis.

Office endometrial sampling for histologic evaluation plays a fundamental role in the diagnosis of abnormal uterine bleeding. Diagnostic dilatation and curettage (D & C) in the operating room under general anesthesia remained the predominant method used to obtain endometrial samples until the early 1980s. In a 1982 reappraisal of D & C, Grimes [16] concluded that "D & C should probably not be the primary method of obtaining samples of endometrium from most patients." This landmark publication moved endometrial evaluation into the gynecologist's office. The development of flexible, disposable suction curettes not requiring external suction generation (Pipelle in the mid-1980s [17] and GynoSampler in 1992 [18], among others) has further facilitated convenient, quick, office-based endometrial evaluation with a sensitivity in diagnosing endometrial cancer in excess of 90% [19,20]. Use of the Pipelle and other similar aspirators is associated with less pain and cramping than with the rigid metal Novak curette [17,20,21]. One disadvantage of endometrial biopsy with use of narrow caliber (3 mm outer diameter) devices, including the Pipelle, is that focal benign intracavitary lesions including polyps and submucosal myomata may be missed [22,23].

Advances in ultrasound technology have led to increased use of vaginal sonography to evaluate abnormal perimenopausal bleeding. A study of 433 women over the age of 39 years who were not clinically menopausal found that unenhanced vaginal sonography was sufficient for evaluating abnormal uterine bleeding in 65% of patients [24]. The remaining 35% underwent saline infusion sonohysterography; 29% of these procedures were performed because of inability to measure the endometrium sonographically, and 71% were performed for endometrial measurement greater than 5 mm. Goldstein et al [24] recommended hysteroscopy with curettage for those patients in whom a focal abnormality was demonstrated on saline infusion sonohysterography.

Saline infusion sonohysterography is playing an increasing role in the evaluation of abnormal uterine bleeding in women in general and in perimenopausal women in particular. This procedure is increasingly replacing diagnostic hystero-

scopy, which was long viewed as the gold standard in the evaluation of intracavitary lesions [6,25]. Compared with sonohysterography, hysteroscopy is a more invasive procedure and does not assess the myometrium. A prospective evaluation of sonohysterography in 233 premenopausal and postmenopausal patients with abnormal bleeding found that the procedure had a sensitivity of 85.7% and specificity of 95.4% in the diagnosis of polyps and submucosal myomas [25].

A comparison of sonohysterography findings in 100 asymptomatic premenopausal women age 30 and older and 80 premenopausal women of the same age with abnormal uterine bleeding found that those with abnormal bleeding had a higher prevalence of polyps (33% versus 10%); intracavitary myomata (21% versus 1%); and intramural myomas (58% versus 13%) [26]. This important study points out that not all intracavitary polypoid lesions are symptomatic. In this study asymptomatic polyps tended to be smaller than those found in women with abnormal bleeding (8.5 versus 13.9 mm, $P = .064$).

Even though their presence seems to reflect ongoing estrogenic endometrial stimulation, most endometrial polyps are benign [27–29]. Among 1415 women aged 23 to 85 who underwent D & C for abnormal uterine bleeding, the prevalence of endometrial polyps was 8.9% (125 of 11415). Of these, 75% were benign; 24% had premalignant changes (complex or atypical hyperplasia); and only two polyps (1.5%), both found in postmenopausal women, had undergone malignant degeneration [29].

Although unenhanced vaginal sonography represents a sensitive method for diagnosing uterine pathology; its specificity is greatly improved by saline infusion [30,31]. A direct comparison of unenhanced and saline infusion sonohysterography in 62 premenopausal women with abnormal uterine bleeding found that specificity was far greater with saline infusion sonohysterography (95% versus 21%) [31]. Nevertheless, because of recent reports suggesting dissemination of endometrial carcinoma cells in the course of hysteroscopy [32,33], presumably reflecting the impact of fluid instillation, it may be prudent to defer sonohysterography until office endometrial sampling has excluded carcinoma.

In the author's practice, after a focused history and pelvic examination, the first evaluation performed in the perimenopausal woman presenting with abnormal uterine bleeding is endometrial biopsy. If the histology demonstrates benign endometrium, including hyperplasia without atypia, the author proceeds with medical management as outlined later in this article. If such management does not result in a satisfactory bleeding profile, the next step is unenhanced vaginal sonography. If endometrial measurements are greater than 4–5 mm, the author proceeds with sonohysterography. Given the absence of large, randomized, controlled trials comparing different evaluation strategies, however, clinicians should use the techniques (including endometrial biopsy, sonohysterography, and office diagnostic hysteroscopy) with which they are most technically comfortable, and which are most accessible and cost effective in their practices for the in-office evaluation of abnormal uterine bleeding in the perimenopausal woman.

In contrast with sonohysterography, hysteroscopy permits direct visualization of the endometrial cavity, identification of polyps and submucosal fibroids,

targeted biopsy procedures, and removal of submucosal leiomyomas and endometrial polyps [34]. Office hysteroscopy has become an easy, safe, rapid, and effective method of intrauterine evaluation [34]. Diagnosis is precise, even with use of narrow hysteroscopes not substantially larger in diameter than the Pipelle catheter [35]. Although highly reliable (approximately 80% agreement with histologic studies [36]) the success of this procedure depends in large part on the technical skill of the operator. A disadvantage of hysteroscopy is that when performed as an office procedure with local anesthesia or no anesthesia, patients may experience considerable discomfort [24]. Consequently, hysteroscopy is often performed under general anesthesia at an ambulatory surgery center [24]. The author reserves hysteroscopy for women in whom intracavitary lesions requiring biopsy or excision have been found with sonohysterography.

Medical management of abnormal uterine bleeding in perimenopausal women

After initial endometrial evaluation hormonal management options include combination oral contraceptives (OCs); combined noncontraceptive estrogen-progestin (oral and injectable); cyclic oral progestins; or continuous progestin (oral, injectable, or intrauterine device [IUD]). The following discussion of these hormonal regimens does not address the contraceptive needs of perimenopausal women, which are covered elsewhere in this issue.

If endometrial proliferation or hyperplasia without atypia is found, progestin-based medical management is indicated, with follow-up office biopsy after 3 to 4 months [15]. If progestin therapy does not result in histologic regression, D & C should be performed before surgical therapy because of the possibility of underlying endometrial malignancy [6,15]. There is nearly a 30% chance that complex endometrial hyperplasia with atypia progresses to cancer if untreated [37]; therefore, hysterectomy represents appropriate surgical management in this setting.

Combination OCs

Until recently, the usual approach for the medical management of abnormal uterine bleeding consisted of cyclic oral progestin, with estrogen added if vasomotor disturbances occurred or withdrawal bleeding ceased [15]. A number of estrogen-progestin options are now available and listed as follows:

Contraceptive Formulations:
- Cyclical
  - Low estrogen dose (≤ 35 μg) combination oral contraceptives
  - Monthly contraceptive injection (medroxyprogesterone acetate 25 mg/ estradiol cypionate 5 mg per injection, Lunelle)
  - Weekly transdermal contraceptive patch (150 μg norelgestromin/20 μg ethinyl, Ortho Evra)
    - estradiol daily)
  - Three-week contraceptive vaginal ring (~ 120 μg etonogestrel/15 μg ethinyl per day, NuvaRing)

- Continuous
  Three-month depot medroxyprogesterone acetate injection (150 mg per injection, Depo-Provera) plus oral or transdermal estradiol
  Levonorgestrel intrauterine device (Mirena) plus oral estrogen

High Progestin Dose Combination Menopausal Formulations:
  Norethindrone acetate 0.5 mg/estradiol 1 mg (Activella)
  Norethindrone acetate 1 mg/ethinyl estradiol 5 μg (femhrt)

Many clinicians consider low-dose combination OCs to be first-line agents for the treatment of abnormal uterine bleeding occurring in otherwise healthy, nonsmoking, perimenopausal women, regardless of contraceptive needs [38]. Studies have shown that OC use regularizes menstrual cycles and decreases menstrual flow [39–41]. In a recent multicenter, randomized, double-masked trial in over 200 women with abnormal bleeding associated with anovulation, use of triphasic norgestimate, 35 μg ethinyl estradiol (EE) (Ortho TriCyclen), improved bleeding patterns in 80% of subjects [42]. A study in 132 symptomatic perimenopausal women found that an OC containing 20 μg of EE and 1 mg of norethindrone acetate (Loestrin Fe 1/20) significantly shortened menstrual cycle duration, decreased variability, and reduced bleeding severity over six cycles of use [43]. During the last three cycles, there also was a significant reduction in the incidence and duration of clots and flooding. The American College of Obstetricians and Gynecologists considers OCs the treatment of choice for anovulatory uterine bleeding [44]. Nonetheless, clinicians should be aware that no combination estrogen-progestin regimen is approved by the Food and Drug Administration for the treatment of abnormal uterine bleeding in perimenopausal or other women.

Because the risk of venous thromboembolism events increases with increasing age [45], some clinicians may be reluctant to use OCs in perimenopausal women. The relative risk of venous thromboembolism associated with OC use, however, does not seem to increase with age [46]. The risk of venous thromboembolism with new low-dose OCs ($\leq$ 35 μg EE), although three to four times higher than that of nonusers, is substantially lower than with the older higher-dose OCs [47]. The OC progestin component also seems to affect the risk of venous thromboembolism [48]. Formulations containing either desogestrel or gestodene (not used in US OCs) are associated with a two-fold-greater risk of venous thromboembolism than those containing levonorgestrel [49].

Cycle control is an important issue for perimenopausal women who are experiencing abnormal uterine bleeding. The OC formulation selected should cause minimal breakthrough bleeding or irregular bleeding [38]. Because of their different estrogen doses and progestin types, OC formulations have different effects on irregular bleeding. Many clinicians prefer OCs containing 20 μg of EE for older reproductive-age women; however, comparisons of OCs formulated with 20 or 30 μg of EE have reported substantially more unscheduled bleeding with the lower EE dose [50,51]. A recent randomized clinical trial found

substantially higher rates of breakthrough bleeding with 20-μg EE norethindrone acetate OC compared with a 35-μg EE norgestimate OC [52].

Two new 25-μg EE triphasic OC formulations, one with desogestrel (Cyclessa) and the other with norgestimate (Ortho TriCyclen-Lo), seem to provide excellent cycle control [53,54]. A 13-month, randomized, double-blind comparison found significantly better cycle control with triphasic norgestimate and 25-μg EE OC than with monophasic norethindrone acetate and 20-μg EE (Loestrin FE 1/20) [54]. Perimenopausal women with menorrhagia may benefit from less frequent menses or even amenorrhea, which can be achieved with an extended OC regimen [55].

Other contraceptive estrogen-progestin options

Other contraceptive estrogen-progestin options to regularize bleeding in perimenopausal women without contraindications to use of combination OCs include the monthly contraceptive injection containing medroxyprogesterone acetate and estradiol cypionate (Lunelle) [56]; a transdermal contraceptive patch (Ortho Evra) [57]; and a contraceptive vaginal ring (NuvaRing) [58,59]. Although use of these formulations should regularize perimenopausal bleeding disturbances, clinicians should be aware that no clinical trials have assessed the use of these combination products in the treatment of irregular bleeding.

Noncontraceptive estrogen plus contraceptive progestin therapy

Some perimenopausal women with abnormal bleeding may not be candidates for combination OCs or other contraceptive estrogen-progestin options because of cigarette smoking, hypertension, diabetes, or migraine headaches [44]. Because combination OC use, advancing age, and obesity each represent independent venous thromboembolism risk factors [46], some clinicians may choose not to use combination OCs in obese perimenopausal women. Although cyclic progestin therapy may be appropriate for some of these women, those with vasomotor symptoms, low bone density, or hypoestrogenism associated with cigarette smoking may benefit more from a combination of estrogen and progestin than from progestin therapy alone. In this setting, older low-dose menopausal combination hormone replacement therapy (HRT) regimens do not suppress ovulation, and tend to make bleeding worse rather than better [38].

Although little if any data address this recommendation, hormonal therapy combining progestin doses sufficient to suppress ovulation in combination with doses of estrogen lower than those in combination OCs represents a useful therapeutic approach. One approach is to use a combination of oral or transdermal estradiol with depot medroxyprogesterone acetate injections. This combined regimen suppresses ovulation, produces amenorrhea over time [60], and treats vasomotor symptoms [61]. Another approach is to use the newer fixed-combination HRT formulations containing estradiol, 1 mg, plus norethindrone acetate, 0.5 mg (Activella), or ethinyl estradiol, 5 μg, plus norethindrone acetate, 1 mg (femhrt). The doses of norethindrone acetate included in these formulations are equivalent to the daily doses of the same progestin in marketed combination OC formulations; accordingly, use of these formulations likely suppresses ovulation.

Both of these newer HRT formulations provide endometrial suppression and good control of bleeding in late perimenopausal and postmenopausal women [62–65]. Perimenopausal women initiating these new low-estrogen high-progestin continuous-combination regimens should be counseled to anticipate the occurrence of irregular spotting or bleeding with eventual amenorrhea.

An advantage of oral or transdermal estrogen plus depot medroxyprogesterone acetate injections and high progestin dose combination menopausal formulations is that they can be continued through menopause because the amount of estrogen provided during the perimenopause continues to be appropriate for the postmenopausal woman.

Progestin-only therapy

Oral progestins. Traditionally, medical therapy for dysfunctional uterine bleeding in perimenopausal women was cyclic oral progestin. The oral progestins available in the United States are medroxyprogesterone acetate (Provera); norethindrone acetate (Aygestin); and norethindrone (Micronor). Table 3 lists suggested dosages, which should be administered for 12 to 14 days each month and result in predictable bleeding. Cyclic progestin therapy reverses hyperplastic changes in most patients [15] and controls irregular bleeding. A reduction of about 40% in menstrual blood loss was reported in one study in which women were given either medroxyprogesterone acetate, 10 mg three times daily from days 5 to 25 of the cycle, or norethindrone, 5 mg/d for 20 days of the cycle [66]. Studies have shown varying effects on bleeding ranging from no change to an increase [67].

Cyclic progestin-only therapy is particularly useful in obese perimenopausal women who are well-estrogenized. After endometrial biopsy (which characteristically reveals proliferative or hyperplastic changes), cyclic progestin therapy for the first 12 to 14 days of each month is initiated. Signs that addition of menopausal doses of estrogen may be indicated in this setting include the occurrence of vasomotor symptoms or cessation of withdrawal bleeding. Some obese perimenopausal women treated with cyclic progestin-only therapy may continue to experience withdrawal bleeding indefinitely. Continuation of progestin therapy in this setting is appropriate; otherwise, endometrial neoplasia may occur [68].

Table 3
Oral, cyclic progestin-only regimens for the treatment of abnormal uterine bleeding in perimenopausal women

Progestin	Tablet Strengths (mg)	Daily Dosage *
Medroxyprogesterone acetate	2.5, 5, 10	5 – 10 mg
Norethindrone acetate	5	2.5 – 5 mg[†]
Norethindrone	0.35	0.7 – 1 mg[‡]
Danazol	50, 100, 200	200 mg

* Administered for 12–14 days each month.
[†] 0.5–1 tablet/d.
[‡] 2–3 tablets/d.

In women with menorrhagia, danazol, 200 mg/d, given daily for one to three cycles or during menstruation significantly decreased menstrual blood loss compared with placebo [69–71]. Side effects, however, such as hirsutism, weight gain, headaches, deepening of the voice, and acne, may make danazol therapy unacceptable to many women.

Levonorgestrel IUD. Another option for progestin-only therapy of abnormal uterine bleeding is the levonorgestrel-releasing IUD (Mirena) that has been available in Europe for more than 10 years and is now available in the United States. A 12-month study in symptomatic perimenopausal women found that the levonorgestrel IUD effectively prevented endometrial proliferation in women treated orally with 2 mg/d estradiol valerate, and reduced uterine bleeding more effectively than the addition of cyclic oral levonorgestrel (250 μg/d) during the last 10 days of each cycle [72].

A small trial in 20 women with menorrhagia found that the levonorgestrel IUD decreased menstrual blood loss 86% after 3 months' use and 97% after 12 months [73]. A comparative study in women with menorrhagia found that the levonorgestrel IUD was as effective in reducing menstrual blood loss to within normal limits as oral cyclic norethindrone, 5 mg three times daily administered on days 5 to 26 of each cycle [74]. Another study in women awaiting hysterectomy found that after 6 months of treatment, a higher proportion of women using the levonorgestrel IUD cancelled the planned surgery compared with those receiving their existing medical therapy [75]. A Finnish study randomized women with menorrhagia referred for hysterectomy to two treatment groups: insertion of the levonorgestrel IUD or hysterectomy [76]. At 1 year of follow-up, patient satisfaction was similar in the two treatment groups. The levonorgestrel IUD can also be used to treat endometrial hyperplasia [77,78].

As with the oral and injectable noncontraceptive estrogen plus high-dose progestin regimens discussed previously, if the levonorgestrel IUD is inserted during the perimenopause, it can remain in place into the menopausal years with the addition of low-dose estrogen for the relief of climacteric symptoms.

Surgical management of abnormal uterine bleeding

Hysterectomy

In the past hysterectomy was viewed as the only definitive cure for benign abnormal uterine bleeding failing to respond to medical treatment. Approximately 600,000 hysterectomies are performed annually in the United States, making this the second most frequently performed major surgical procedure among reproductive-age women [12,79]. Data for the period from 1988 to 1993 indicate that among women aged 35 to 54, the diagnosis most often associated with hysterectomy was uterine leiomyoma [12]. Concomitant oophorectomy was performed most often among women aged 45 to 54, 76% of whom underwent such surgery [12]. Although operative mortality is low (6 per 10,000 procedures)

[80], postoperative complications during hospitalization occur in approximately 30% of patients [81].

Endometrial ablation

Since the 1980s, various techniques for hysteroscopic endometrial resection and ablation have been developed as effective, safe, cost-saving alternatives to hysterectomy for the treatment of menorrhagia [6,82,83]. Techniques requiring substantial training, operative hysteroscopy with electrosurgical or laser endometrial ablation are associated with complications in about 6% of cases [84]. Thermal balloon endometrial ablation (ThermaChoice) is simpler to perform [82,85,86]. When compared with hysteroscopic rollerball ablation in a randomized, multicenter trial, follow-up data for 239 women treated for menorrhagia indicated that the thermal balloon technique was equally effective and possibly safer [87].

Women frequently receive pretreatment with danazol or gonadotropin-releasing hormone analogues before endometrial ablation. A recent prospective, randomized, controlled comparison, however, found no significant differences in outcomes between women undergoing delayed ablation with gonadotropin-releasing hormone analogue pretreatment and those treated immediately [85].

Clinicians using endometrial ablation in the treatment of abnormal uterine bleeding in perimenopausal women should keep several issues in mind. First, as with any treatment in this setting, perimenopausal women with abnormal uterine bleeding should undergo endometrial histologic evaluation before endometrial ablation. Second, thermal balloon ablation does not involve visualization of the endometrial cavity and does not effectively treat abnormal bleeding caused by endometrial polyps or submucosal fibroids. Accordingly, clinicians should evaluate the endometrial cavity with sonohysterography or diagnostic hysteroscopy before thermal balloon ablation or any other blind endometrial destructive therapy. Likewise, clinicians planning hysteroscopic endometrial ablation should be prepared to resect any polypoid lesions encountered intraoperatively. Finally, clinicians should recognize that endometrial ablation does not successfully treat abnormal uterine bleeding caused by anatomic lesions located in the uterine wall: intramural fibroids or adenomyosis.

Vasomotor disturbances

Vasomotor disturbances (hot flashes and cold sweats) represent symptoms commonly reported by perimenopausal women [88]. Although many women begin to experience hot flashes at the onset of irregular perimenopausal bleeding, as many as 40% report that hot flashes started while menstrual cycles were still regular [89]. Usually the occurrence of hot flashes increases slowly before the transition to perimenopause, at which time it peaks, and then gradually declines during the postmenopause [90,91]. Approximately 10% to 13% of premenopausal, 37% to 50% of perimenopausal, 20% to 62% of postmenopausal women,

and 15% of postmenopausal women on HRT report vasomotor symptoms [90,91]. Hot flashes are far more common among premenopausal women with confirmed premenstrual syndrome or menstrual cycle–related disorders [92], and perimenopausal women with a history of these disorders during their reproductive years [91,93]. There is wide variation in the severity and duration of vasomotor symptoms, with some women experiencing severe hot flashes for many years [94].

Although the mechanism of hot flashes is not completely understood, they seem to originate in the hypothalamus and are triggered by estrogen withdrawal or deficiency [95,96]. The frequency with which hot flashes are reported is associated with increasing levels of follicle-stimulating hormone and decreasing levels of estradiol [91]; however, not all reported hot flashes are related to estrogen deficiency [15].

Differential diagnosis of vasomotor disturbances

The patient's age and menstrual history (menstrual cycle irregularity, oligomenorrhea, or amenorrhea) are good indicators of whether hot flashes and sweating are related to the climacteric [97]. Flashes, however, can be caused by other conditions (Table 4) [92,98]. In addition, cardiovascular disease should be ruled out if hot flashes are associated with palpitations and feelings of anxiety [4]. Clinicians should also recognize that hot flashes in some women reflect emotional problems rather than hormonal phenomena [15].

Table 4
Medical conditions that mimic hot flashes

Systemic diseases
Thyroid disease
Pheochromocytoma
Carcinoid syndrome
Systemic mast cell disease
Leukemia
Pancreatic tumors
Renal cell carcinoma
Neurologic causes
Stress and anxiety
Brain tumors
Orthostatic hypotension
Migraines
Parkinson's disease
Spinal cord injury
Emotional flushing
Alcohol
Drugs (vasodilators, calcium channel blockers, bromocriptine, tamoxifen, raloxifene, gonadotropin-releasing hormone agonists)
Food additives (nitrites, sulfites, red pepper, or capsaicin)
Eating

Treatment of vasomotor disturbances in perimenopausal women

More than 40 randomized, controlled trials have shown that estrogen therapy improves vasomotor symptoms in menopausal women [99]. Low-dose estrogen replacement with 0.3 mg of conjugated estrogens [100] or 25 μg of transdermal estradiol alone or in combination with norethindrone acetate provides symptomatic relief for many patients [101,102]. Women using estrogen alone, however, are at increased risk of endometrial cancer [68]. Good evidence suggests that progestins reduce vasomotor symptoms [99]. Well-controlled studies in menopausal women have found resolution or improvement of vasomotor symptoms with use of medroxyprogesterone acetate (oral or injectable) [103,104] and megestrol acetate [105].

Most often a combination of estrogen and progestin is used to treat climacteric symptoms in nonhysterectomized perimenopausal women. Low-dose combination OCs is a highly effective option for the relief of hot flashes in healthy, nonsmoking perimenopausal women [43,106]. Another option that has been shown to provide effective contraception and relief of vasomotor symptoms and nocturnal sweating in perimenopausal women is transdermal estradiol (0.05 mg/d for 21 days) combined with an oral progestin, such as medroxyprogesterone acetate (10 mg/d in the last 12 days) [107]. Other effective options for the treatment of vasomotor symptoms in women in whom use of contraceptive doses of estrogen is contraindicated include oral high progestin dose combination menopausal formulations [62–64] or injectable medroxyprogesterone acetate combined with estrogen. If hormonal therapy fails to control vasomotor symptoms, clinicians should consider emotional issues as a possible cause.

Recently, interest in nonhormonal approaches for the treatment of vasomotor symptoms has increased. There is growing evidence that certain selective serotonin-reuptake inhibitors effectively treat hot flashes [108–110]. These and other pharmacologic and nonpharmacologic options for the relief of vasomotor symptoms in perimenopausal women are discussed elsewhere in this issue.

Vulvogenital changes and sexual dysfunction

Perimenopausal women commonly report vulvogenital changes, including vaginal dryness or itching and dyspareunia [111], all of which can contribute to sexual dysfunction [112,113]. Indeed, among perimenopausal women, the most commonly reported sexuality-related physical complaint is discomfort during intercourse, which may reflect vaginal dryness. Changes in skin sensitivity and hormone levels during perimenopause can decrease the desire for sexual contact and the response to sexual stimulation [112,114].

Atrophic genital changes, which are reported by 75% or more of postmenopausal women, are thought to be related to estrogen depletion [115]. Often the first change reported is reduced vaginal lubrication during sexual arousal [4,111]. The prevalence of vaginal dryness increases from 16% in women aged 39 and older with regular menstrual cycles to 40% to 45% in postmenopausal women [94].

Usually, vaginal dryness is attributed to declining estrogen levels; however, this symptom is not reported by 55% of postmenopausal women [94], and an estimated 10% to 25% of women receiving systemic HRT experience genital atrophy [116]. In addition to vaginal dryness and other vulvogenital changes, diminished interest in sexual relations may be the result of physical conditions, such as irregular or heavy menses, hot flashes, insomnia, chronic diseases (eg, diabetes, cardiovascular disease), and genitourinary malignancy [113], or emotional issues, such as concerns about body image [114].

Clinicians should be proactive in treating women with vulvogenital symptoms or sexual dysfunction associated with atrophy. Estrogen replacement therapy, typically in vaginal forms, is the mainstay of treatment for genital atrophy and atrophic vaginitis [117]. A recent meta-analysis showed that vaginally administered low-dose estrogen is as effective as systemic estrogen, although these preparations do not cause the same increase in serum levels of estrone or estradiol [118]. Compared with systemic estrogen, local therapies have a more rapid effect on vaginal blood flow, which relieves symptoms more rapidly [119].

Traditionally, local estrogen creams have been used to treat symptomatic atrophic changes; however, creams can be messy and many women find them unpleasant or difficult to use. New low-dose vaginal estradiol formulations, such as twice weekly vaginal tablets (Vagifem) and the 3-month vaginal ring (Estring) [120–122], are effective for treating vulvogenital atrophy and provide important options for women who do not wish to or cannot take estrogen systemically, and those who experience symptoms of genital atrophy despite hormone replacement [117]. These formulations have greater acceptance among patients than older vaginal creams [123], which are expected to improve compliance and symptom control [122]. Although no relationship between estradiol levels and female sexuality has been found in menstruating women [124,125], the improved vaginal physiology in perimenopausal and postmenopausal women treated with estrogen is likely to improve libido in some, and is not expected to have a negative impact on sexuality [126].

Summary

The gynecologic problems associated with the perimenopause and detailed in this review represent common and often vexing concerns for women during this transition. By heeding the evidence-based approaches to evaluation and treatment described herein, clinicians can improve the health and lives of their perimenopausal patients.

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Obstet Gynecol Clin N Am
29 (2002) 475–493

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Reproductive hormones and cardiovascular disease Mechanism of action and clinical implications

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The effects of estrogens and progestogens on reproductive tissues and menopausal symptoms are unambiguous. There is considerable controversy regarding effects on other tissues, however, particularly in the cardiovascular system. Epidemiologic data suggest that premenopausal women are largely protected from coronary heart disease (CHD) compared with aged-matched men [1]. This phenomenon, sometimes referred to as *female protection*, is more accurately characterized as a delay in disease onset, with CHD events in women lagging behind those of men by about 10 years [2]. Both natural and surgical menopause are associated with increased risk of CHD [3], further suggesting beneficial effects of ovarian hormones. In addition, estrogen replacement therapy (ERT) is associated with about a 30% to 50% decrease in CHD risk in postmenopausal women [4,5] and about a 50% decrease in atherosclerosis in animal models [6–9]. The foregoing findings suggest beneficial effects of estrogens on the cardiovascular system. Surprisingly, randomized trials in postmenopausal women with preexisting CHD have found no benefits of combined hormone replacement therapy (HRT) [10].

One possible resolution for the apparent contradictory findings between studies relating to primary and secondary prevention of CHD relates to the effects of estrogen on atherosclerosis. Atherosclerosis, the primary cause of myocardial infarction and a major contributor to stroke, progresses over decades. It is

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likely that the clinical events affecting postmenopausal women have their beginnings in the premenopausal years. This conclusion is supported by the Pathobiological Determinants of Atherosclerosis in Youth study, which reported the presence of raised lesions in the coronary arteries of one third of women by age 34 [11]. It has been suggested that estrogen may inhibit the development and early progression of atherosclerosis but have a net neutral or negative effect on advanced lesions [12]. This hypothesis implies that early exposure to exogenous estrogen, as occurs for example in the context of estrogen-containing oral contraceptives (OCs), should be protective against the development of atherosclerosis or CHD. It might also be expected in premenopausal individuals that there would be an association between naturally occurring variation in estrogen and risk of atherosclerosis and CHD. Further, it is possible that estrogens may have adverse effects on other risk factors associated with cardiovascular disease (CVD), such as thrombosis. Early studies with OCs found that these adverse effects were dose-dependent. Recent studies with HRT suggest similar findings, which may have great relevance to the early adverse effects in randomized trials. These possibilities are considered in detail next.

OCs and atherosclerosis

Some of the concern regarding cardiovascular effects of OCs is related to the theoretically adverse effects on plasma lipoproteins (eg, they increase concentrations of low-density lipoprotein cholesterol [LDLC] and decrease high-density lipoprotein cholesterol [HDLC]) [13]. Studies with cynomolgus monkeys (*Macaca fascicularis*) have found that OCs do not increase progression of atherosclerosis, but instead decrease lesion extent by about 70% in those receiving ethinyl estradiol alone compared with controls [14]. Levonorgestrel alone had no effect and combined treatment was intermediate.

One mechanism for the beneficial effects of OCs on atherosclerosis may be caused by direct beneficial effects of estrogens on the artery wall. One potential site for estrogen effects on atherogenesis is the uptake and metabolism of LDL by cells of the artery. Arterial LDL metabolism can be assessed in vivo. LDL particles are radiolabeled and injected into monkeys after relatively short periods of treatment to allow investigation of the hormonal effects before treatment effects on atherosclerotic lesions. Using such an approach, it was found that both monophasic and triphasic OCs reduced arterial LDL accumulation about 70% despite adverse effects on plasma lipoprotein concentrations [15].

Naturally occurring estrogen deficiency, atherosclerosis, and CHD

Although few studies in women directly examine the possibility that variation in endogenous estrogen may contribute to atherosclerosis risk, several pieces of evidence are suggestive of such an association. First, early menopause is

associated with an increased risk of CHD, as is a history of menstrual irregularity [16]. Also, in comparison with normally cycling controls, irregularly menstruating women have elevated plasma fibrinogen concentrations (a risk factor for atherosclerosis) and a thickened arterial intima [17]. Finally, premenopausal women with angiographically confirmed coronary disease have significantly lower plasma estradiol concentrations than do controls [18].

Studies involving female monkeys consuming an atherogenic diet provide direct evidence on the relationship between endogenous estrogen and risk of atherosclerosis. Naturally occurring estrogen deficiency occurs relatively frequently in such animals when housed in social groups, affecting approximately that half of the individuals that is subordinate in the dominance hierarchy. A number of studies demonstrate that, in comparison with their dominant counterparts, subordinate individuals experience an acceleration of coronary artery atherosclerosis and display impaired coronary vascular dilation in response to acetylcholine. In contrast, pregnancy (a hyperestrogenic condition) results in an almost complete inhibition of atherosclerosis [19,20]. Importantly, these subordinate, estrogen-deficient females, in comparison with their dominant counterparts, develop exacerbated atherosclerosis and display impaired coronary vascular dilation in response to acetylcholine [19,21,22].

A recently completed lifetime (premenopausal-postmenopausal) study in this species further confirms the significance of premenopausal estrogen status in relation to the risk of CVD. In the premenopausal portion of this study, animals were placed in social groups of five or six animals each and fed an atherogenic diet. In addition, half of the animals were treated with a triphasic OC [20]. After 2 years, a portion of right iliac artery (as a surrogate for the coronary artery) was removed from each animal and atherosclerosis extent determined. All animals were then ovariectomized and continued to consume an atherogenic diet for 3 years (the postmenopausal segment), after which time the experiment ended and coronary artery atherosclerosis extent was evaluated. During this latter portion of the experiment, two thirds of animals were treated with conjugated equine estrogens (CEE) or soy phytoestrogens, whereas the remainder was untreated.

In the premenopausal segment of the experiment, dominant animals (treated or not) have relatively little atherosclerosis (Fig.1). Among the subordinate or at-risk animals, those treated with OCs are indistinguishable from the dominants. In contrast, untreated subordinates experienced a significant, 60% increase in atherosclerosis. As in previous experiments, untreated subordinates were also estrogen-deficient in comparison with dominants. Taken together, these results support the hypothesis that social subordination potentiates atherogenesis by ovarian impairment.

The intent of the postmenopausal segment was to determine whether premenopausal social status and OC exposure influenced the extent of coronary artery atherosclerosis observed postmenopausally, and whether any such influences were modified by postmenopausal HRT [23]. The results showed that the interaction of premenopausal social status and OC exposure predicted coronary artery atherosclerosis ($P = .02$). Subordinate animals not receiving OCs developed twice the

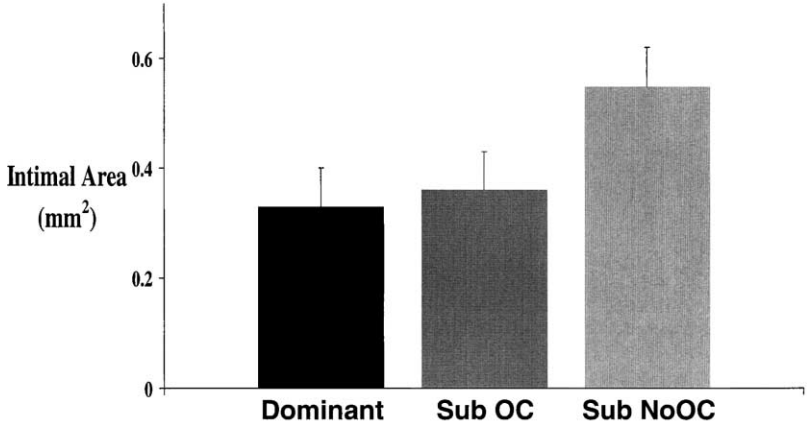

Fig. 1. Iliac artery atherosclerosis in premenopausal dominant (treated or not treated with oral contraceptive) and subordinate monkeys. Subordinates treated with oral contraceptives were indistinguishable from dominants; untreated subordinates had significantly increased lesion extent. Sub = subordinate; OC = oral contraceptive. (*Data from* Kaplan JR, Adams MR, Anthony MS, et al. Dominant social status and contraceptive hormone treatment inhibit atherogenesis in premenopausal monkeys. Arterioscler Thromb Vasc Biol 1995;15:2094–100.)

coronary atherosclerosis of similarly untreated dominants ($P < .01$). The increase was diminished by premenopausal OC exposure, because there was significantly greater coronary artery atherosclerosis in untreated subordinates in comparison with their OC-treated counterparts ($P < .01$). These effects occurred across all postmenopausal treatment groups and were independent of variation in plasma lipids ($P > .20$). The pattern of results resembles closely the effect on iliac artery atherosclerosis depicted in Fig. 1. These data suggest that premenopausal hormonal and associated behavioral conditions significantly influence atherosclerosis, both premenopausally and postmenopausally.

OCs and other CVD risk factors

Recent studies of OCs in current use indicate that the risk of cardiovascular sequelae (ie, venous thromboembolism, myocardial infarction, and stroke) is low because of reduction in steroid dosages, particularly the estrogen component, over the past 40 years [24]. Age, obesity, surgery, genetic predisposition, such as activated protein C resistance, and immobilization are some of the risk factors associated with venous thromboembolism [25]. For users of OC age 40 to 44 years, the attributable risk is small in the range of 11 to 36 events per 100,000 women annually with a case fatality rate in the range of 1% to 3% [26]. The higher incidence estimates are for women using preparations containing gestodene or desogestrel. It is unclear why these two progestins alter the risk compared with other progestins, particularly levonorgestrel.

The OC users who are nonsmoking and normotensive do not have an increased risk of myocardial infarction. The presence of these risk factors and age, however, act synergistically to increase the risk among OC users. Despite this synergy, the attributable risk of myocardial infarction for users of OC age 40 to 44 years is only about 48 events per 100,000 women annually [26]. Unlike venous thromboembolism, however, the case fatality rate is about 30%. OC use has also been reported to increase risk of cerebral venous and sinus thrombosis, particularly in those with inherited hyperthrombotic conditions [27].

Stroke is even more uncommon in the 40-to 44-year-old age group with an attributable risk of about three to seven cases per 100,000 OC users annually [26]. Cigarette smoking and hypertension are modifiable risk factors for both ischemic and hemorrhagic stroke; use of preparations with 50 μg of estrogen or higher and migraine headaches are additional risk factors for ischemic stroke. Eliminating risk factors among OC users substantially reduces the risk of ischemic stroke and virtually eliminates the risk of hemorrhagic stroke [25,26].

Although OCs increase the risk of venous thrombosis in women [25,26], the risk of arterial thrombosis is less clear. Studies in monkeys suggest that there is no increased risk [28]. Premenopausal monkeys consumed an atherogenic diet for approximately 2 years with either no additional treatment or with combined triphasic OC. Arterial thrombosis was evaluated with a standardized stenosis-injury procedure in the carotid artery. A reduction in the incidence of thrombosis was found in OC-treated animals compared with controls. The effect of hormonal agents on venous thrombosis has not been investigated in monkeys to the authors' knowledge.

HRT effects and CVD

Although CVD is an uncommon cause of morbidity and mortality in the premenopausal age group, among postmenopausal women it is the most common cause of death. In 1997, cardiovascular disorders accounted for about 500,000 deaths in US women, more deaths than the next 14 causes combined [29]. Since the mid-1980s over 30 observational studies have evaluated the association between either ERT or HRT and CHD [4,5,8,30]. Overall, a 30% to 50% reduction in risk of various CHD sequelae for either ERT or HRT users compared with nonusers has been found. Although there are numerous potential mechanisms that have been identified supporting these observational studies, recently published clinical trial reports have suggested that the relationship between estrogen and progestin use in postmenopausal women and CHD is complex and that risk or protection may vary depending on clinical circumstances.

The Heart and Estrogen/Progestin Replacement Study (HERS) Research Group determined in a randomized clinical trial that, among postmenopausal women at an average age of 67 years with pre-existing CHD, use of a continuous regimen of CEE and medroxyprogesterone acetate (MPA) compared with placebo was ineffective overall in preventing secondary events (eg, myocardial infarction

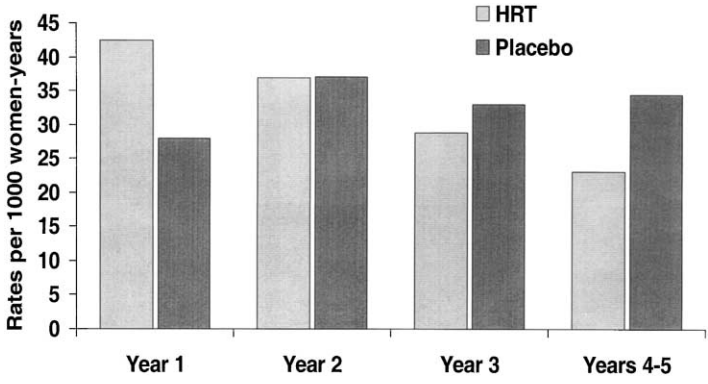

Fig. 2. Primary coronary heart disease events in women from The Heart and Estrogen/Progestin Replacement Study (HERS); a secondary prevention trial. Overall, there was no significant difference between placebo (*solid bar*) and hormone replacement therapy ([HRT] *open bar*) treatment. Within the overall null effect, however, there was a significant time trend ($P = .009$) with more CHD events in the HRT group in year 1, and fewer in years 4 and 5. (*From* Wagner JD. Effects of sex steroid treatment on the cardiovascular system. Infertil Reprod Med Clin N Am 2001;12:511–33; *Data from* Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA 1998;280:605–13.)

or death) [10]. There was an increased rate of CHD and thromboembolism among HRT users compared with placebo in the first year of follow-up. By the fourth year the rate of CHD events in the HRT group was below that of the placebo group (Fig. 2). Further analysis of the HERS data indicated that the increased CHD risk was seen primarily in women with low lipoprotein (a) (Lp[a]) levels at baseline, whereas women with initially high Lp(a) levels seemed to benefit most from HRT as the study progressed [31]. In particular, the Lp(a) levels showed significant declines and the rate of CHD events decreased. These findings suggest that there may be groups of susceptible women who experience secondary coronary events perhaps caused by effects of estrogen on coagulation factors initially. The remaining women then show reduced risk because of the beneficial effects on plasma lipoproteins.

The Estrogen Replacement and Atherosclerosis (ERA) randomized clinical trial evaluated progression of coronary artery changes in postmenopausal women with angiographically verified CHD at baseline [12]. After about 3 years of follow-up, neither CEE alone nor CEE in combination with MPA slowed the progression of coronary atherosclerosis as determined angiographically in these women with pre-existing disease. A preliminary report from the Papworth Hormone-Replacement Therapy Atherosclerosis Study also showed no benefit from transdermal estradiol alone or in combination with norethindrone in reducing CHD events in women with pre-existing disease [32].

It is unclear from existing clinical trial data whether HRT alters risk of CHD in women without CHD. A pooled analysis of 22 clinical trials that were designed primarily to evaluate other clinical effects of HRT showed a nonstatistically sig-

nificant increase in risk of cardiovascular events in women using HRT [33]. An interim analysis of the Women's Health Initiative (WHI) clinical trial involving postmenopausal women treated with CEE alone or in combination with MPA versus placebo indicated that there was a small increase in the number of myocardial infarctions, strokes, and thromboembolism among treated women in the first 2 years of the study [34]. The overall rate of events was less than 1%, however, and the trends seemed to diminish over time. Because of the short duration of the existing prospective clinical trials involving women without preexisting CHD, it is too early to determine whether the findings of observational studies demonstrating beneficial effects of HRT will be confirmed or refuted.

As with OC use, venous thromboembolism is more common in HRT users compared with nonusers [10]. The risk is highest in the first year of use. Overall, the attributable risk is about 20 additional cases per 100,000 users annually [35,36]. Pulmonary embolism, the most significant form of venous thromboembolism, is also increased among HRT users. The attributable risk among women age 50 to 59 years, however, is only about five additional cases per 100,000 women-years [37].

Four cohort studies have evaluated risk of stroke among HRT users [38–41]. Although one study showed no protection related to use [41], the other three demonstrated either reduction in stroke mortality of 47% to 63% or reduction in stroke incidence of at least 30% [38–40]. A more recent report from the Nurses Health Study [5] found that the risk of stroke was related to daily estrogen dose. Those taking 0.625 or 1.25 mg/d CEE had increased risk, whereas those taking 0.3 mg/d had lower risk. As with OCs, use of higher estrogen doses may be more prone to prothrombotic risk. A recent report from HERS showed no effect of combined CEE and MPA on stroke or transient ischemic attack [42]. In light of the finding from the Nurses Health Study, however, results may have been different if a lower dose of hormones had been chosen.

Results from the prospective studies (ie, HERS and ERA) suggest that differences in either the study design (secondary prevention studies), the older age of the women at the time of initial treatment, or the relatively short study time (3 to 4 years) compared with most of the observational studies, which have generally examined first events occurring in younger women who have been examined for longer duration, may explain some of the differences. A recent report from the Nurses' Health Study followed 85,941 women over a 14-year period [30]. During this time, the incidence of CHD declined by 31%. A number of risk factors changed during this period, including a decrease in smoking, an increase in use of HRT, and an improvement in diet. Taken together, the changes in these variables explained a decline of 21%, or two thirds of the decline in CHD incidence. These favorable changes were offset by an increase in obesity, which explained an 8% increase in CHD incidence. The large sample size, the high rate of follow-up, and the detailed information collected on these women strongly supports the notion that both HRT and a more healthy lifestyle can decrease the incidence of CHD in women.

The mechanisms of how estrogen provides cardioprotection are complex and likely multifactorial [8,9]. Plasma lipid-dependent mechanisms account for about

25% of the effect and include increased HDLC levels, decreased LDLC levels, and decreased Lp(a) levels. Estrogen also lowers fibrinogen and improves insulin sensitivity. It has antioxidant activity and suppresses LDL degradation and accumulation in the artery wall. Estrogen also increases vasodilation through endothelium-dependent mechanisms [43,44] and through effects on the renin-angiotensin system [45,46]. These lipid-independent mechanisms account for about 75% of the cardioprotective effects of estrogens [8,47].

Studies in monkeys have found that estrogens are potent inhibitors of primary atherosclerosis progression. One of the earliest studies of ERT in monkeys determined the effects of physiologic estradiol and progesterone replacement therapy [6]. Monkeys were ovariectomized and randomly assigned to receive one of three treatments administered subcutaneously using a sustained-release Silastic implant: no HRT (control); continuously administered 17β-estradiol; or continuously administered 17β-estradiol plus cyclic progesterone. Monkeys consumed an atherogenic diet and treatment for 30 months after which coronary artery atherosclerosis was assessed. Both estradiol- and estradiol-progesterone–treated animals exhibited approximately one half the amount of coronary artery atherosclerosis compared with control animals, while not affecting plasma lipoprotein concentrations because of the parenteral route of delivery.

A subsequent study [7] was designed to test a commonly prescribed HRT in women. Monkeys were treated with continuous oral CEE, 0.625 mg/d human equivalent alone, MPA, 2.5 mg/d human equivalent alone, or CEE continuously combined with MPA as opposed to control animals who received no HRT. After treatment for 30 months, unopposed CEE therapy resulted in a 72% reduction in average plaque size compared with control animals (Fig. 3). MPA treatment alone

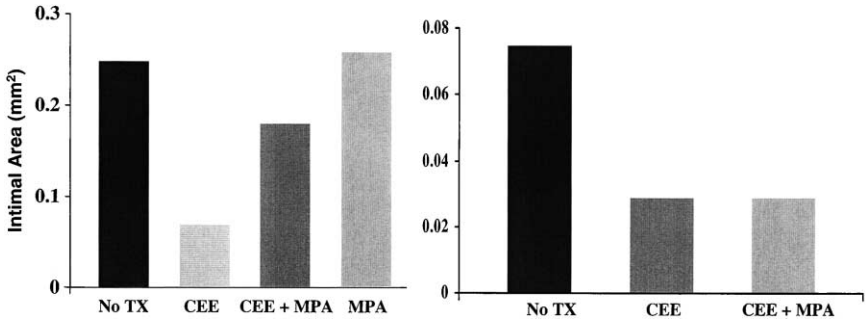

Fig. 3. Primary prevention of coronary artery atherosclerosis in monkeys. In study one (*left*), conjugated equine estrogens (CEE) significantly decreased atherosclerosis compared with no Treatment (TX). (*Data from* Adams MR, Register TC, Golden DL, et al. Medroxyprogesterone acetate antagonizes inhibitory effects of conjugated equine estrogens on coronary artery atherosclerosis. Arterioscler Thromb Vasc Biol 1997;17:217–21.) Medroxyprogesterone acetate (MPA) and CEE + MPA were not significantly different from no TX. In study two (*right*), CEE and CEE + MPA equally decreased atherosclerosis compared with no TX. (*Data from* Clarkson TB, Anthony MS, Wagner JD. A comparison of tibolone and conjugated equine estrogens effects on coronary artery atherosclerosis and bone density of postmenopausal monkeys. J Clin Endocrinol Metab 2001;86:5396–404.)

had no effect on atherosclerosis and those receiving combined CEE and MPA treatment had an intermediate effect.

Subsequent studies have verified the protective effects of CEE [48,49] but not the attenuation with MPA [48]. In this more recent study [48], CEE and CEE plus MPA equally reduced coronary artery atherosclerosis extent by 62% (see Fig. 3). The major difference between the two studies was the delivery of the hormones. In the second study, the HRT dose was given as a divided dose twice daily. Concentrations of hormones reaching the liver at any one time were essentially halved compared with once-daily delivery, but the hormone levels were likely maintained for a longer duration. It seems that these differences are physiologically quite relevant. For example, in the more recent study, MPA did not completely prevent the CEE-induced proliferation of the endometrium [50] in contrast to the prior trial using once-daily dosing of hormones [51]. This could have important clinical implications regarding overall ERT-HRT treatment recommendations.

Estrogen and mechanisms for arterial effects

As with OCs, the uptake and metabolism of LDL by cells of the artery are reduced with postmenopausal estrogens. Physiologic doses of estradiol and cyclic progesterone treatment reduced by about 70% the degradation and subsequent accumulation of LDL in the coronary arteries compared with ovariectomized monkeys given no HRT. Because of the parenteral replacement therapy, plasma lipid, lipoprotein, or apoprotein concentrations were not affected, suggesting a direct effect on the artery wall [52]. In a subsequent study using the same techniques, oral esterified estrogens with and without methyltestosterone also decreased coronary artery LDL accumulation by about 70% in ovariectomized monkeys [53]. In this study, aortic lipid peroxidation products were decreased, suggesting estrogen's antioxidant activity may be involved with decreased metabolism of modified LDL particles by intimal macrophages.

Because LDL, and especially modified LDL, accumulates in the artery wall, monocyte adhesion and chemotaxis are stimulated, resulting in further formation of macrophage foam cells. Estrogen may inhibit atherogenesis by decreasing monocyte adhesion and inhibiting expression of number of adhesion molecules, including vascular adhesion molecule–1, intracellular adhesion molecules–1, and E-selectin [44,54,55]. Estrogen may also decrease monocyte chemotaxis because it was found to suppress monocyte chemoattractant protein–1 in vivo [56]. In addition to decreasing monocyte adhesion and migration into the artery, estrogen may also directly affect the metabolism of LDL by macrophages decreasing LDL accumulation and foam cell formation [57]. A recent report found that combined CEE and MPA and CEE and micronized progesterone treatments decreased E-selectin, intracellular adhesion molecules–1, vascular adhesion molecule–1, monocyte chemoattractant protein–1, and tissue factor antigen and plasminogen activator inhibitor–1 [58]. In addition, ERT reduces

angiotensin converting enzyme activity and mRNA [45] and down-regulates Angiotensin type 1 (AT_1) receptor levels [46], which may provide vasorelaxant effects. The effects on markers of inflammation, hemostasis, and fibrinolysis inhibition and vascular relaxation may provide additional nonlipid-mediated mechanisms for cardioprotection.

Although a number of markers of inflammation are decreased with ERT and HRT, C-reactive protein (CRP) is increased. CRP has been shown to be an independent risk factor for CVD in women [59]. Of particular concern is that serum CRP increases after estrogen or estrogen and progestin treatment in women [60,61]. The synthesis of CRP in the liver is regulated by interleukin-6, and these levels have been shown to be lower in women with HRT [62]. It is unclear if this increase in CRP is associated with any early increase in CHD risk described in the prospective trials.

Endothelial damage may increase LDL uptake and atherogenesis. A number of studies have looked at effects of endothelial damage induced by balloon catheter injury in rabbits and how estrogen affects progression of atherosclerosis under these conditions [63–65]. As in previous studies in rabbits, estradiol inhibited aortic cholesterol in noninjured areas of the aorta; this was independent of plasma cholesterol levels because rabbits were ''clamped'' at similar plasma cholesterol levels. Areas with injury to the endothelium, however, had increased cholesterol content with no effect of estradiol [63]. In a subsequent study, injured areas of the aorta that were re-endothelialized had increased cholesterol compared with uninjured areas with similar cholesterol content between control and estradiol treatment. In de-endothelialized areas of the injured aorta, however, estradiol treatment actually increased cholesterol content [64]. The antiatherogenic effect of estradiol was present, absent, or reversed depending on the state of the arterial endothelium.

The localization of sex steroid hormone receptors in the cardiovascular system was instrumental to the study of mechanisms for hormone action. Estrogen receptor (ER) expression levels have been shown to vary among normal and atherosclerotic coronary arteries obtained from premenopausal and postmenopausal women [66]. Most (71%) specimens obtained from normal arteries stained positive for ER expression, whereas a minority (32%) of atherosclerotic arteries stained positive for ER expression. The relationship between ER expression and atherosclerosis was more evident in premenopausal women. A growing number of vascular effects have been attributed to ER [44].

Recently, two ER subtypes have been identified; ERα, the classic ER, and ERβ [67]. Both subtypes are distributed throughout the body, including the cardiovascular tissues [67–69]. A recent study found that ERβ was the predominant ER in human vascular smooth muscle, particularly in women [69]. Other studies found that after endothelial denudation of rat carotid arteries, ERα mRNA remained expressed at low levels, whereas ERβ mRNA increased [70]. This suggests there may be differential regulation of these receptors with disease states or concentration. Also, whereas estradiol binds with equal affinity to both receptor subtypes, some estrogens, particularly the phytoestrogens, have relatively

higher affinity for ERβ [71], a fact that may prove useful clinically in the design of compounds that selectively bind one ER subtype.

Although the vascular effects of ER are becoming better characterized, the role of progesterone receptors needs to be determined. Further, the addition of a progestagen to the ERT regimen may result in changes in both ER and progesterone receptors levels. These changes have not been characterized in the vasculature, but have been studied in the breast and uterus. In the uterus, estrogen up-regulates ER mRNA, whereas progesterone down-regulates its own receptor and the ER [72]. The arterial effects mediated through the ER may not be the same during ERT versus HRT.

Selective ER Modulators and CVD

Although there are a number of reasons why ERT may be beneficial in reducing CVD, there are still a number of disadvantages to conventional ERT including continued menstrual bleeding and fear of breast and uterine cancer. As such, selective ER modulators (SERMs), such as raloxifene, are being investigated as potential alternatives. Raloxifene, for example, has been shown to act as an estrogen agonist in bone and in plasma cholesterol metabolism but as an estrogen antagonist in mammary gland and uterine tissue [73,74]. Because SERMs could, theoretically, protect against endometrial hyperplasia without the use of concomitant progestogen and without an increased risk of breast cancer, there has been considerable interest in determining the potential role of SERMs in CVD.

A number of animal studies have suggested beneficial effects of SERMS on atherosclerosis. Tamoxifen, one of the first SERMS studied, seems to have mixed agonist and antagonist activity in monkeys fed an atherogenic diet for 2 years. Tamoxifen reduced coronary artery atherosclerosis compared with no treatment by 50% compared with a 70% reduction with CEE in monkeys [75]. Although CEE resulted in coronary artery dilation in response to an acetylcholine challenge, tamoxifen treatment resulted in vasoconstriction, similar to monkeys receiving no treatment [43]. These divergent results, both at the level of the artery, suggest that estrogen action at the artery wall is mediated differently for atheroprotection compared with vasodilation, perhaps by different ERs.

Animal studies regarding raloxifene have revealed mixed results. In one study [76], ovariectomized, cholesterol-fed rabbits were treated with raloxifene, 17β-estradiol, or placebo. At the conclusion of the study, the extent of aortic atherosclerosis was reduced by one third in the raloxifene-treated group and by two thirds in the estradiol-treated group, as compared with control animals. In contrast, studies in monkeys have not found beneficial effects of raloxifene on atherosclerosis. Clarkson et al [49] compared the effects of CEE or raloxifene at 1 and 5 mg/kg/d with placebo in a group of ovariectomized monkeys fed a moderately atherogenic diet. Similar to the results achieved in women taking raloxifene, LDLC levels were reduced and HDLC levels remained unaffected. No

evidence of atheroprotection, however, was found with raloxifene compared with a 70% reduction in coronary artery plaque size with CEE versus controls.

A report comparing raloxifene with CEE on CVD risk factors in women has been published. [77]. Raloxifene and CEE both reduced LDLC and fibrinogen, whereas only CEE increased HDLC and decreased plasminogen activator inhibitor−1. Whereas CEE produced an increase in CRP, raloxifene did not. Studies addressing effects of raloxifene on CHD risk in women were evaluated in the Multiple Outcomes of Raloxifene Evaluation trial. After four years, raloxifene theory did not affect risk of CVD events in the overall cohort, but did significantly reduce events in the subset of women with increased CVD risk [78].

Results from human trials regarding SERMS and CHD are urgently needed to investigate further their potential future role as HRT replacements. Results from one trial investigating droloxifene have suggested beneficial effects on blood flow in postmenopausal women [79]. Droloxifene, which is structurally similar to tamoxifen, resulted in reductions of LDLC and Lp(a) but no change in HDLC. Droloxifene, like estrogen, also reduced fibrinogen but produced no estrogen-like changes in plasminogen. Interestingly, whereas tamoxifen did not improve coronary vasodilation in monkeys, forearm blood flow was improved with droloxifene similar to estrogen in women. The forearm blood flow studies did not address endothelial-dependent responses, however, as assessed by the acetylcholine challenge in monkeys.

Tibolone is not actually a SERM but a synthetic steroid that on metabolism has estrogenic and progestogenic-androgenic properties and has been used in Europe for climacteric symptoms and osteoporosis. Because of the metabolism to a progestogenic metabolite, no additional progestogen is needed. Although the benefits on postmenopausal symptoms and osteoporosis are similar to conventional HRT, there seem to be no adverse effects on the endometrium or breast cancer risk, making this therapy appealing [80,81]. The effects of tibolone on CVD are less clear. Although tibolone reduces some CHD risk factors, such as Lp(a), triglycerides, and fibrinogen, it also reduces plasma HDLC concentrations [82,83] and may not be cardioprotective. In ovariectomized rabbits, tibolone reduced atherosclerosis extent but there were no reductions of HDLC and 50% to 70% reductions in total cholesterol [84]. A recent report in ovariectomized monkeys found no protection against atherosclerosis progression with tibolone treatment compared with a 60% decrease with CEE [48]. Unlike studies in women where the HDLC reductions are generally around 30% [82,83], however, there was up to a 50% reduction in HDLC concentrations in the monkeys.

Soy isoflavones and CVD

Many women are interested in a nutritional approach to CVD reduction. Epidemiologic, cross-cultural, and numerous animal studies support the notion that soy consumption is cardioprotective [85−88]. For example, Japanese men who consume relatively large amounts of soy have about one sixth the risk of

CHD as US men [88]. In a meta-analysis, the effects of soy on plasma lipids and lipoproteins were reviewed [86]. Both men and women had substantial reductions in plasma triglycerides, total cholesterol, and LDLC, and modest to minimal increases in HDLC concentrations.

Dietary soy protein contains the isoflavones genistein and daidzein, which have been proposed to mediate some of the beneficial effects. These compounds are structurally similar to estradiol, but whereas estradiol binds similarly to both ERα and ERβ, the isoflavones bind with relative greater affinity to ERβ compared with ERα. The relative expression of ERα and ERβ differs greatly between individual tissues [71], perhaps playing a role in tissue-specific responses to estrogens and phytoestrogens as with SERMS.

Crouse et al [89] evaluated the effects of a soy protein supplement containing various levels of isoflavones (3, 27, 37, or 62 mg) on plasma lipid and lipoprotein concentrations compared with a casein supplement. All supplements contained equivalent amounts of protein. Compared with casein, the soy supplement containing 62 mg of isoflavones significantly reduced both total cholesterol and LDLC. In addition, isoflavone concentrations had a dose-response effect on lowering of LDLC, suggesting isoflavones are responsible for the lipid lowering.

Monkey studies have found beneficial effects of isoflavones on plasma lipid and lipoprotein responses [87]. Plasma lipid and lipoprotein responses were compared in monkeys fed a diet with the protein source from soybeans either containing the soy isoflavones (high isoflavones) or one with most of the isoflavones removed by alcohol extraction (low isoflavones). The high-isoflavone diet reduced the total and non-HDLC concentrations in both male and female monkeys and increased the HDLC concentrations in females. Further, the soy isolate containing isoflavones resulted in marked inhibition of coronary artery atherosclerosis in male cynomolgus monkeys relative to casein-fed monkeys or monkeys fed soy protein isolate from which the isoflavones had been extracted.

A study by Clarkson et al [90] compared the effects of isoflavones with CEE. Postmenopausal monkeys were fed an atherogenic diet with the protein source being either soy protein depleted of the isoflavones, soy protein with the isoflavones, or a third group fed soy protein depleted of the isoflavones but also given CEE. The group consuming soy protein with the isoflavones had better lipoprotein responses than the other groups. In addition, the soy protein with isoflavones improved atherosclerosis extent compared with the isoflavone-depleted soy, but in general, not quite as well as CEE treatment.

The effect of soy protein in combination with ERT is important to consider, because many women using ERT-HRT may also be eating soy. A study in monkeys [91] found improvements in a number of CHD risk factors with both soy protein consumption and estradiol treatment. In particular, the consumption of soy protein compared with casein-lactalbumin resulted in significantly lower total cholesterol and higher HDLC, yet had no effect on triglyceride concentrations. Both soy and estradiol improved different aspects of glucose and insulin metabolism. Together soy and estradiol resulted in greatest improvements in

decreasing body fat content, increasing antioxidant activity, and decreasing aortic cholesterol content.

Although the benefits of soy protein on plasma lipids and CVD seem to be mediated by isoflavones, of major public health importance is whether the same benefits can be obtained with pills containing isolated isoflavones. Studies in people [92,93] and monkeys [94] have found no beneficial effect on plasma lipid and lipoprotein concentrations with soy isoflavone supplementation. It is still unclear if isoflavones are the active ingredient in soy or if there is some interaction between the soy protein and isoflavones required for greatest benefit.

Summary

The bulk of the experimental data suggest beneficial effects of estrogen (both premenopausal use of OCs and postmenopausal use of ERT-HRT). An intriguing finding from the monkey studies is that social subordination, which induces estrogen deficiency in female monkeys, accelerates atherosclerosis premenopausally and predicts extent of postmenopausal atherosclerosis. This effect can be inhibited by exogenous estrogen, premenopausally. The results suggest that more effort on detecting and regulating premenopausal ovarian dysfunction may be justified.

A complication in understanding estrogen action may be the result of varying extents of arterial damage. For example, primary prevention studies in both postmenopausal animals and women have provided strong evidence of atheroprotection with a variety of estrogens. In contrast, the results of secondary prevention studies [10,12] have in general suggested little cardioprotection with either ERT or HRT. Studies in rabbits suggest the antiatherogenic effect of estrogen may not be present when the endothelium is damaged [64]. The state of the endothelium may be critical for some estrogen actions.

For those effects of estrogen that require the ER, be it ERα or ERβ, the presence of the receptor may vary with age, disease state, or type of hormone therapy. If continuous combined HRT therapy decreases ER in the artery as it does in the uterus, this may eliminate those estrogen actions requiring the ER, but not others. Older women who have not been exposed to estrogens for many years may be more sensitive to some estrogen effects, and may need lower doses of ERT-HRT. Recent reports suggest that lower doses of estrogens maintain beneficial effects on lipoproteins and coagulation factors [95], while also requiring lower doses of progestogens to protect the uterus [96]. These beneficial findings are very promising in light of the improvements in CHD risk and decreased stroke risk reported with low-dose estrogens [5]. It will be interesting to see if CRP is increased with lower doses of estrogens and whether these changes are associated with increased early risk of CHD. Perhaps older women with CHD are also more obese, may have diabetes, and may be more susceptible to inflammatory and thrombotic effects of higher doses of estrogens.

There are many questions left unanswered. It is hoped that some of the answers may come from the WHI, which is a large prospective trial assessing ERT and HRT. The age range is also relatively large and may be able to determine if older women respond differently than younger women. Some initial data from the WHI have been made available suggesting a small increased risk in the first 2 years and a trend for decreasing risk in the last months of the first 2 years [34]. Just recently, the CEE + MPA arm of the study was stopped early by the data and safety monitoring board as the overall health risks exceeded benefits with increases in both breast cancer and CVD [97]. The remainder of the study groups including an estrogen-only arm, are expected to continue until 2005.

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Bone metabolism and the perimenopause Overview, risk factors, screening, and osteoporosis preventive measures

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Nearly 60 years ago, Albright et al [1] recognized the increased propensity of women to develop weak fragile bones and spinal crush fractures in the decade that follows natural or surgical menopause. At that time, rickets was the predominant public health hazard affecting bone health. As diets and vitamin supplements have improved and as the longevity of men and women has increased, osteoporosis has replaced rickets as a major public health concern. It is now estimated that 28 million Americans are osteoporotic, 80% of who are women. The annual economic cost of osteoporotic fractures in the United States is $10 to 14 billion, and the global impact is certain to be much larger [2]. The mortality rate of osteoporotic hip fractures in the elderly is 15%, and half of those who sustain a hip fracture never return to their previous lifestyle. It has been estimated that a 50-year-old white woman has a 32% lifetime risk of developing a vertebral fracture, a 15% risk of Colles' fracture, and a 16% risk of suffering a hip fracture [3,4]. Given a 15% mortality rate for hip fractures, her risk of dying from hip fracture is about 3%, which is equivalent to the risk of dying from breast cancer. The importance of this epidemic is underscored by the establishment of an organization dedicated to research, and patient education in this area, the National Osteoporosis Foundation. Obstetricians and gynecologists as primary care providers for women are in a key position to prevent, identify, and treat osteoporosis and to reduce the social and economic impact of this debilitating condition.

The fact that postmenopausal women are inordinately affected by osteoporosis strongly suggests a causal link to estrogen deficiency. A prolonged state of estrogen deficiency, whether caused by natural or surgical menopause, or by hypogonadotropic states (eg, gonadotropin-releasing hormone agonist therapy,

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hypothalamic amenorrhea, and hyperprolactinemia), is associated with bone demineralization [5]. Recently, it has become clear that congenital estrogen deficiency in men is also associated with severe osteoporosis, which is reversed with estrogen replacement [6–8]. The exact molecular mechanisms by which estrogen exerts its influence on bone density are not clear. Bone tissue is in a constant state of remodeling whereby bone resorption by osteoclasts and bone formation by osteoblasts are modulated by mechanical and hormonal factors throughout childhood and adult life, including bone stresses and strains; serum calcium and phosphorus levels; and circulating levels of parathyroid hormone (PTH), thyroid hormone, vitamin D, cortisol, and sex steroids. The current state of knowledge indicates that estrogen deficiency increases bone resorption by osteoclasts probably through activation of local tissue cytokines and prostaglandins [9]. Bone formation increases to a lesser degree favoring net resorption, mostly in trabecular bones (spine, pelvis, and distal radius). Cortical and skull bones are spared in contrast to osteoporosis caused by hyperparathyroidism. With declining estrogen levels of the perimenopause there is an accelerated phase of bone loss of 2% to 3% annually, which continues for 6 to 7 years. At the end of this interval approximately 15% of trabecular bone mineral density (BMD) is lost and affected bones become prone to fracture with minimal trauma. Cortical and trabecular bone loss continues thereafter at an annual rate of approximately 1% and is thought to be caused by the aging process [10].

The ultimate aim of prevention and treatment of osteoporosis is the prevention of debilitating fractures. The annual incidence of hip and spinal fractures in the elderly general population is estimated at 0.5% to 2% [11]. This low incidence means that large long-term longitudinal multicenter trials are needed to show that an intervention is effective in reduction of fracture rates. There is no good evidence that any therapeutic intervention in the general postmenopausal population is useful for primary prevention of fractures. There is good evidence, however, that certain antiresorptive therapies reduce fracture rates in patients with skeletal risk factors (eg, osteopenia, osteoporosis, and previous fractures) and nonskeletal risk factors (eg, advanced age and propensity to fall). Another approach commonly used in osteoporosis research is to measure fluctuations in surrogate indices of fracture risk (eg, bone density and bone turnover markers in response to various interventions). A decrease in bone turnover markers or an increase in bone density in response to a particular intervention is assumed to translate into decreased fracture risk later in life.

Screening for osteoporosis

Risk factors for osteoporotic fractures in women are many, some of which are modifiable, whereas others are not. They include age and years since menopause; menopause before age 45; lifelong history of low calcium intake; alcoholism; decreased visual acuity; frail physical or mental health; history of recurrent falls; inadequate physical activity; white race; low body mass; family history of osteo-

porosis or fractures; personal history of fractures; smoking; residence in northern latitudes; intake of benzodiazepines; anticonvulsants; corticosteroids or heparin; dietary protein and calcium insufficiency; and chronic medical illnesses, such as diabetes, renal disease, arthritis, and thyroid disease [12,13]. The common pathway by which most of these risk factors manifest is low bone density, which is the single most important risk factor for osteoporotic fractures. Screening for osteoporosis is recommended by the National Osteoporosis Foundation for all women over 65 and for women age 50 to 65 who have one of the previously mentioned risk factors in addition to menopause [14]. All postmenopausal women who present with fractures should have a test to confirm the diagnosis and determine disease severity. Women who are considering therapy for osteoporosis prevention may want to have a bone density test if it facilitates their decision. Screening of premenopausal women is not recommended, although osteoporosis can exist in this population. Exceptions can be made in patients with several risk factors and a personal or strong family history of fragile bones.

The World Health Organization (WHO) has defined osteoporosis based on bone density scans at the hip and spine using dual-energy x-ray absorptiometry (DEXA). This is a noninvasive measure that takes 5 minutes to complete, is associated with radiation exposure of less than 5 mrem, and has a 1% precision. Bone density is reported as a T score, which is the number of standard deviations from the mean bone density in sex- and race-matched young normal adults. By definition, osteoporosis is a T score of -2.5 and osteopenia is a T score between -1 and -2.5. Based on this definition approximately 17% of healthy postmenopausal women have spinal osteoporosis, 16% have femoral neck osteoporosis, and 12% have total hip osteoporosis [13]. It should be noted that for every standard deviation below the mean peak bone mass, the risk of fracture doubles (ie, with a T score of -1 the risk of fracture is doubled, and with a T score of -2 the risk is fourfold). Another measurement less commonly used is the Z score, which is the standard deviation from the age-, sex-, and race-matched normal mean. A Z score of more than 1 point below the mean should alert to the possibility that other causes of osteoporosis (eg, renal, metabolic, endocrine, gastrointestinal, hematopoietic, and connective tissue disease) may exist.

One of the shortcomings of the WHO definition of osteoporosis is that the standardized curves for peak and age-specific bone mass were developed using mostly white women. Caution should be used when interpreting bone density measurements in women of other races where peak bone mass and fracture rates may be different or may have yet to be determined. In a study from Thailand, for example, a significantly higher proportion of postmenopausal women would have been classified as osteoporotic if WHO standards had been used instead of Thai standards [15]. Another shortcoming is that DEXA scanners are expensive and heavy to transport, which limits their use to specialized medical centers. More versatile technologies for osteoporosis screening are available and approved by the Food and Drug Administration (FDA) (eg, hand and wrist bone assessment). They are useful for screening women over 65 years old, but their use in the decade after menopause is fraught with a significant risk of false-negative

screens. This is caused by the fact that perimenopausal bone loss affects mostly trabecular bone, which predominates in the axial and not the appendicular skeleton [16]. One notable exception is the heel, which is rich in trabecular bone. Preliminary research has found good correlation between quantitative heel ultrasound and central DEXA measurements [17]. Further improvements in precision and additional validation and standardization are needed before wider acceptance of this and other peripheral technologies for screening and monitoring therapy in perimenopausal women. At this time, DEXA is the most useful tool for osteoporosis screening in perimenopausal women in the United States.

Prevention of osteoporosis: children and adolescents

Optimal peak bone mass is the best buffer against the erosive impact of senescence and estrogen deficiency later in life. A positive correlation exists between calcium intake in the teenage years and adult bone density [18]. This suggests that adequate calcium intake is essential to achieve the optimal genetically determined peak bone mass for every child and adolescent. Other benefits of calcium include a possible reduction in risks of colorectal cancer and hypertension later in life. A National Institutes of Health consensus conference in 1994 determined the optimal daily elemental calcium intake to be 800 mg in children and 1200 mg in adolescents [19]. Dairy products are the main source of calcium, because an 8-oz serving of milk contains 350 mg of elemental calcium. Various commercially available cereals and fruit juices are now fortified with calcium, although the bioavailability of calcium from nondairy sources is not certain. It should be noted here that lactose intolerance does not develop before age 5 and should no longer be considered an impediment to optimal calcium intake from dairy products. Randomized controlled studies have shown that self-described lactose-intolerant people can tolerate one 8-oz serving of milk daily without significant side effects [20,21]. Alternate sources of calcium for lactose-intolerant people include fermented dairy products (eg, yogurt and hard cheeses). Excessive intake of carbonated cola beverages in adolescent girls has been associated with a fivefold increase in the risk of bone fractures [22]. It is unknown whether the mechanism for this association includes osteoporosis. In addition to calcium, physical activity has been shown to have beneficial effects on bone density in children and should be encouraged [23]. Vitamin D requirements in childhood have been difficult to measure; however, supplementation with 400 to 800 IU/d seems prudent in instances where the risk of vitamin D deficiency exists (eg, children living in northern latitudes not exposed to enough direct sunlight, breast-fed children, and those who do not consume vitamin D–fortified cow's milk). This position is endorsed by the Canadian Pediatric Society [24].

Pregnancy and breast-feeding have been shown to cause a transient decrease in BMD, which is reversible after cessation of breast-feeding [25]. Use of combination oral contraceptive pills by women over 40 has been noted in two retrospective studies to be associated with a lower risk of postmenopausal

osteoporosis and fractures [26,27]. A randomized 12-month trial of oral contraceptive pill use versus hormone replacement therapy (HRT) in healthy postmenopausal women found that oral contraceptive pill use suppressed bone turnover markers and improved femoral neck BMD significantly more than standard HRT [28]. Whether this translates into long-term reduction in fracture risk is speculative at this time. Nevertheless, these studies suggest an important noncontraceptive benefit of oral contraceptive pill use in perimenopausal women using oral contraceptive pills. As to progestin-only contraceptive methods, WHO studies in older adults have shown that there is no appreciable decline in BMD and that the small declines in some studies are reversible [29]. One possible exception is the long-term use (> 5 years) of depo medroxyprogesterone acetate. Young adolescents who have not yet attained peak bone mass and who have used depo medroxyprogesterone acetate for a long time have lower BMD values at various skeletal sites, although it is not known if this translates into increased osteoporotic fracture risk later in life [30,31].

Preserving bone density in postmenopausal women

Dietary deficiencies in calcium and vitamin D are common in women over 65, and could lead to an increase in PTH and bone demineralization. Supplemental calcium and vitamin D have proved useful for protection of bone density and reduction of fracture risk in the elderly [32–34]. Measurement of serum levels of 25-hydroxyvitamin D is useful in the elderly and in women whose dietary and geographic circumstances put them at risk for vitamin D deficiency. Levels under 10 ng/mL identify those who benefit most from supplementation with 400 to 800 IU of vitamin D. The adult recommended daily allowance of 1000 mg of elemental calcium should be maintained in postmenopausal women on HRT and increased to 1500 mg in those not on HRT [19]. The sole use of calcium and vitamin D supplements, although effective for preservation of bone mass in women over 65, has not proved to be an effective strategy for the prevention of the accelerated phase of bone loss related to estrogen deficiency in women under 65 [35].

Chronic alcohol abuse has an adverse effect on bone, the mechanism of which is multifactorial and not entirely known [36,37]. Moderate consumption of alcohol, however, has not been associated with an adverse effect on bone [38]. Caffeine intake has been linked to low bone mass in postmenopausal women, but further research in this area is needed to find out whether this association is causal [39–41]. Smoking seems to have an adverse effect on bone and on fracture risk [42] and may eliminate the protective effect of postmenopausal HRT on bone [43]. Two small trials have shown that regular physical activity preserves bone density and muscle mass and improves dynamic balance and muscle strength in menopausal women [44,45]. This in theory could also reduce the risk of falls and fractures. Other practical measures to reduce the risk of falling and fractures in the elderly include improving visual acuity (eg, cataract surgery) and removing obstacles and tripping hazards in the living quarters.

Table 1
Various interventions for prevention and treatment of postmenopausal osteoporosis

Intervention	Cost per dose ($)[†]	Monthly cost ($)	FDA approval for therapy*	FDA approval for prevention*
Calcitonin	2	60–70	Yes	Yes
Alendronate	2.12	60–70	Yes	Yes
Residronate	1.8	60	Yes	Yes
Etidronate	5	25	No	No
Raloxifene	2.11	60–65	Yes	Yes
Equine estrogens	0.5–1	15–30	Yes	Yes
Oral contraceptives	1–1.5	30–45	No	No
Transdermal estradiol	3–7	28–35	Yes	Yes
Oral estradiol	0.5–1	15–30	Yes	Yes
Esterified estrogens	0.5–1	15–30	Yes	Yes
Calcium, 1 g	0.05	1.5	No	No
Vitamin D, 400 IU	0.02	0.6	No	No
Fluoride	0.05	1.5	No	No

[†] Figures are based on price lists provided by the Boston Medical Center Pharmacy in February 2001.

* FDA approval is for use in postmenopausal women only.

In addition to these nonpharmacologic measures, the National Osteoporosis Foundation recommends preventive pharmacologic treatment to reduce fracture risk in postmenopausal women with T scores below -2, or below -1.5 if other risk factors coexist [15]. A number of therapies listed in Table 1 have been approved by the FDA for both prevention and treatment of osteoporosis. Other therapies, which are promising but not approved, are also listed and discussed next.

Sex steroids

The benefits of estrogen in prevention of postmenopausal osteoporosis have been known since the 1950s [46]. More recent observational studies have found that postmenopausal estrogen use reduces spinal and nonspinal fracture rates with the biggest protection noted in current users and early users (ie, those who used estrogen within 5 years of onset of menopause) [47–49]. Prospective studies looking at surrogate indices of bone turnover (eg, bone markers and bone density measurements) have shown that estrogen replacement suppresses bone turnover and improves bone density in the spine and hip [50,51]. Progestins, commonly used as an adjunct to estrogen for endometrial protection, do not seem to lessen the effects of estrogen on bone or to enhance it [52]. Randomized trials with fracture rates as the end point of estrogen therapy are scant. The few that have been published support the contention that estrogen use reduces vertebral fracture risk in osteoporotic women [53] but not in the general population [54]. In one randomized controlled trial from Denmark, primary prevention of forearm fractures was demonstrated with estrogen replacement in recently menopausal women [55]. A more recent meta-analysis of several published and nonpublished randomized controlled trials found a 33% reduction in nonvertebral fractures

among HRT users under age 60 [56]. Despite the proved benefits of estrogen, poor compliance with its use is a major obstacle to realization of these benefits on bone. The main concerns with long-term estrogen therapy are the recurrence of vaginal bleeding and the presumed increase in the risk of breast cancer [57]. Lower-than-conventional doses of estrogen replacement, which may be more acceptable to women, have been shown to improve bone density and suppress bone turnover; however, no fracture data are available [58,59]. Other strategies to improve long-term compliance with estrogen have been reviewed in a recent North American Menopause Society consensus conference, with patient education being a most important feature [60].

There is no evidence that androgens play any role in bone homeostasis after peak bone mass is achieved in men or women. In fact, high endogenous androgen levels in estrogen-deficient men did not protect them from severe osteoporosis [7,8]. It seems that estrogen is the main sex steroid influencing bone health in both sexes after peak bone mass is attained. Although some studies have shown a small short-term advantage of androgen supplementation on bone density in menopausal women, there are no long-term studies or fracture studies to indicate that androgen supplements offer added benefits to estrogen in prevention of osteoporosis. There is also no evidence that adding androgens to conventional HRT offers any additive bone conservation benefits in surgically menopausal women. The use of androgens in postmenopausal HRT, however, may have other benefits (eg, improved sexual function, improved sense of well being, and endometrial atrophy), all of which may improve compliance with HRT [61]. Tibolone, a synthetic steroid with mixed estrogenic, androgenic, and progestational activity commonly used in Europe for climacteric symptoms, has protective effects on bone mass, and is associated with a low rate of vaginal bleeding [62]. Although this feature may improve compliance with its use, there are concerns about its adverse effects on lipid profiles and it is not yet approved in the United States.

The impact of age-related decline in serum dehydroepiandrosterone on bone health is currently unknown. At age 70, the circulating level of dehydroepiandrosterone is 10% to 20% of levels in young adults. This has led to theories that declining dehydroepiandrosterone levels may be linked to the aging process and that dehydroepiandrosterone supplements may help reverse or stop aging-related changes in many organs including bone. There is some evidence from short-term trials that oral and transdermal dehydroepiandrosterone supplementation decreases bone turnover and improves bone density in postmenopausal women [63,64]. There is also some evidence that dehydroepiandrosterone supplementation alters the circulating levels of some cytokines (insulin-like growth factor–1 and interleukin-6) that are implicated in bone turnover [65]. Whether these are direct effects of dehydroepiandrosterone or ones mediated by the tissue conversion of dehydroepiandrosterone to estrogen is not clear. Although these preliminary studies are interesting, there are not enough data to suggest that dehydroepiandrosterone supplementation in osteopenic postmenopausal women reduces fracture rates.

Selective estrogen receptor modulators

Raloxifene

The main evidence for a protective benefit of raloxifene on bone in osteoporotic women comes from the Multiple Outcomes of Raloxifene Evaluation trial [66] in which 7705 postmenopausal women with osteoporosis were randomized to receive raloxifene or placebo and followed over 36 months. Biochemical markers in the treatment group showed that raloxifene slows bone turnover to a rate similar to that in premenopausal women and caused a 2% to 3% increase in bone density in the spine and the hip. There was also a significant 30% to 50% reduction in the incidence of new vertebral fractures in the raloxifene-treated women. All women took calcium and vitamin D supplements daily suggesting that the benefits of raloxifene were additive to those of calcium and vitamin D. Other advantages of raloxifene include the lack of endometrial stimulation [67], a favorable alteration in serum markers of coronary artery disease, and a potential reduction in risk of breast cancer. Side effects of therapy included increased frequency of hot flashes and leg cramps, and a twofold to threefold increased risk of venous thromboembolism similar to that of HRT.

Bisphosphonates

Bisphosphonates bind to bone hydroxyapatite and reduce osteoclast activity and bone resorption. They have been proved to reduce the risk of vertebral and hip fractures in patients with low bone mass and in patients with previous fractures but not in patients without skeletal risk factors. Those benefits are additive to the ones derived from calcium and vitamin D supplements.

Etidronate

This first-generation bisphosphonate has been shown to improve bone density and reduce new vertebral fractures when used cyclically at a dose of 400 mg daily for 2 weeks every 3 months in postmenopausal women with osteoporosis [68]. The studies done on etidronate do not have enough power to evaluate the effects on nonvertebral fracture risk. Etidronate is approved for treatment of osteoporosis in Canada and Australia but not in the United States.

Alendronate

The usefulness of this agent in fracture reduction in postmenopausal women has been evaluated in the Fracture Intervention Trial, an ongoing randomized controlled trial in which thousands of patients with osteoporosis or prior osteoporotic vertebral fracture received either placebo or alendronate [69,70]. The results so far indicate a 30% to 50% reduction in new fracture rates. Other US and multinational trials in osteoporotic patients with and without prior fractures have shown that alendronate decreases bone turnover; improves bone density by up to 6% at multiple sites; and reduces fracture rates of the hip, spine, and wrist by about 50%. Unlike estrogen replacement therapy, it has no effects

on the breast or the uterus. The most commonly reported side effect of alendronate is dyspepsia, which occurs in about 5% of users. Because food and other drugs may interfere with absorption and bioavailability, it is recommended that the drug be ingested on an empty stomach with water only and that patients remain upright for 30 minutes after ingestion. The discontinuation rate of alendronate in several studies was about 7.5%, which was similar to rate of discontinuation of the placebo. A recent trial showed that increases in bone density continue to accrue into the sixth and seventh year of treatment with alendronate and that bone density is maintained for at least 2 years after discontinuation of therapy [71,72]. In women who are not compliant with daily administration of a drug, a more convenient once-a-week dosing of alendronate (70 mg for treatment and 35 mg for prevention of osteoporosis) has been shown to produce changes in bone density and suppression in bone turnover markers comparable with the daily-dose regimen with no increase in the rate of gastrointestinal side effects. Although this once-weekly dose has not been evaluated for its fracture reduction efficacy, it has been approved by the FDA for osteoporosis prevention and treatment.

Residronate

Large prospective trials have shown that residronate reduces the risk of vertebral and nonvertebral fractures, including hip fractures, in postmenopausal women with osteoporosis [73,74]. The magnitudes of the reduction in fracture risk are comparable with alendronate, although alendronate induces larger reductions in bone turnover markers and larger increases in BMD at various sites. The mechanism of action is similar to that of alendronate. The safety, efficacy, and side effects are similar for both drugs.

Calcitonin

Salmon calcitonin intranasally or subcutaneously at a dose of 200 IU daily increases bone density, reduces bone turnover, and significantly reduces the risk of new vertebral fractures in postmenopausal women with osteoporosis [75]. Compared with alendronate, calcitonin seems to be less effective in protecting BMD and suppressing markers of bone turnover [76]. It is approved for treatment, but not prevention of osteoporosis. Because of its unique analgesic effects, it can be very useful in promoting early mobilization in postmenopausal osteoporotic women with painful acute vertebral fractures [77].

Fluoride

Pharmacologic doses of fluoride may augment bone density in the spine and reduce spinal fracture rates, but some studies have shown that appendicular skeleton may be demineralized during fluoride therapy leading to an increased risk of nonvertebral fractures [78]. Other studies have shown that long-term intermittent slow-release form of fluoride has a low incidence of side effects,

improves spinal and femoral neck bone density, and reduces new vertebral fractures in women with osteoporosis without demineralizing the radial shaft [79]. Because of lingering concerns, the role of sodium fluoride is currently uncertain and its use is neither recommended nor approved for prevention and treatment of postmenopausal osteoporosis.

Complementary and alternative therapies

Soy and other plant products have received significant attention for their potential therapeutic role in prevention of coronary artery disease and breast cancer and in treating hot flashes in postmenopausal women. The soybean isoflavones, genistein and daidzein, have been shown to protect against bone loss in ovariectomized rodents [80]. This has led to suggestions that oral dietary and supplemental intake of these phytoestrogens may be beneficial in osteoporosis prevention. One recent randomized controlled trial, however, found that ipriflavone, a synthetic isoflavone derivative, does not prevent bone loss or affect biochemical markers of bone metabolism in women with postmenopausal osteoporosis [81]. Because there are better proved drugs for treatment of postmenopausal osteoporosis, the use of phytoestrogens for this purpose cannot be recommended at this time. Moreover, countries where diets are rich in soy products (eg, China) have the same problem with osteoporosis as do Western societies, particularly as their population ages and becomes more urbanized [11]. The lower risk of hip fractures observed among Asian women with comparable bone densities may be caused by racial differences in the geometry of the hip axis rather than to soy-rich diets [82,83]. There is no credible evidence that dietary enrichment with soy products in the general population of postmenopausal women offers a protective bone effect.

Anabolic agents and combination therapies

Newer anabolic agents are being evaluated for treatment of osteoporosis (eg, insulin-like growth factor–1, the statins, and intermittent low-dose PTH) [84]. Because of their different mechanism of action, these agents may prove to be useful adjuncts to antiresorptive therapies in treating severe osteoporosis. In fact, PTH 1-34, which is currently awaiting FDA approval, has been shown to improve spinal bone mass and reduce vertebral and nonvertebral fracture rate in women with postmenopausal osteoporosis [85].

Therapeutic regimens combining two antiresorptive agents have also been evaluated, particularly the combination of estrogen and alendronate [86,87]. There are synergistic benefits on bone density with the combination therapy, but it is not clear whether this small advantage in bone density translates into added protection against fractures. Another theoretical advantage to combining estrogen with a second antiresorptive agent is that smaller doses of estrogen may be used with lower risks and side effects. Obviously combination therapies may allow individualization of therapy to suit the needs and risk profiles of patients and

improve their compliance, but they need to be evaluated in randomized trials to ascertain their efficacy in postmenopausal osteoporosis.

Monitoring the response to antiresorptive therapy

Monitoring response to antiresorptive therapy is important for detection of nonresponders who may benefit from further evaluation or a change in therapeutic strategy. It has been estimated that 1% to 2% of women on HRT continue to lose bone at an accelerated rate [88]. This may be caused by genetic factors (eg, polymorphisms in vitamin D receptors and estrogen receptor alpha [89–91]), or to overlooked metabolic conditions (hyperthyroidism, hyperparathyroidism, and steroid intake). Two main factors limit the frequency of monitoring with DEXA. One has to do with the precision of DEXA measurement, which is in the order of 1%, and the other has to do with the intrinsic biology of the bone remodeling process, whereby a long lead time is required to observe a response and determine the true direction of change [92]. Because of these facts, repeat testing to assess response should be performed no sooner than 18 to 24 months after initiation of antiresorptive therapy.

Markers of bone formation (eg, serum osteocalcin and bone alkaline phosphatase) and those of bone resorption (eg, urinary collagen cross-links) are noninvasive and inexpensive means by which response to antiresorptive therapy can be assessed. Single measurements of these markers are not helpful clinically in predicting future bone densities. Serial measurements over time, however, are more predictive of long-term BMD response [93]. For example, a 33% decline from baseline value of the urinary collagen cross-link, CTX, after 3 to 6 months of HRT carries an 87% probability that a positive BMD response is observed after 2 years of therapy [94]. This may serve as a sensitive early forecast of therapeutic efficacy, which could help the clinician in deciding whether to stay the course or change the therapeutic regimen. Some of these turnover markers have already been approved by the FDA for assessment of treatment effectiveness in Paget's disease. Ongoing research and validation studies are likely in the near future to lead to the clearance of bone turnover markers for use in other metabolic bone disorders (eg, osteoporosis).

Summary

In summary, FDA-approved therapies for prevention and treatment of osteoporosis are all antiresorptive agents. There are no approved therapies at this time that stimulate bone formation, although one such agent (PTH) is awaiting approval. Screening perimenopausal women at risk should identify osteopenic women early in the menopause before the accelerated bone loss of estrogen deficiency causes further irreversible erosion in bone density. The National Osteoporosis Foundation advocates initiating therapy to reduce fracture risk in

postmenopausal women with T scores below − 2 in the absence of risk factors and with T scores below − 1.5 if other risk factors are present. Estrogen, alendronate, residronate, and raloxifene have all been shown to reduce the incidence of radiographic vertebral fractures in women at risk. Only alendronate and residronate have been shown in large randomized trials to reduce the incidence of nonvertebral fractures including hip fractures in women with postmenopausal osteoporosis. These antiresorptive therapies provide benefits above and beyond those of calcium and vitamin D alone. There is insufficient published evidence from randomized controlled trials convincingly to support a role for soy products, androgens, calcitonin, or fluoride in prevention of postmenopausal osteoporosis or reduction of fracture rates in women at risk.

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Perimenopausal use of reproductive hormones Effects on breast and endometrial cancer

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Breast and endometrial cancers are common neoplasms influenced by hormonally regulated reproductive events. For example, the incidence of breast cancer, the most common malignancy in women, depends partly on the timing of menarche, pregnancy, and menopause [1–4]. Endometrial cancer incidence is also affected by reproductive factors, including oligomenorrhea [5,6]. There is well-founded concern that these two cancers may be associated with use of reproductive hormones [7–10]. Even a small association from cause-effect is clinically relevant because oral contraceptives (OCs) and hormone replacement therapy (HRT) are among the most frequently prescribed drugs in the United States [11].

The theoretical possibility, however, that use of reproductive hormones increases the risk of reproductive cancers does not suffice for evidence. Indeed, proving that changes in cancer incidence might be caused by exogenous hormone use is a difficult challenge, especially in context of use during the perimenopause. Women with perimenopausal use of OCs are a minority in studies of oral contraception, because prescriptions peak between 25 and 30 years of age and decline thereafter [2]. Few perimenopausal women are involved in studies of HRT, because use of HRT generally occurs after age 50 [11]. Furthermore, the published evidence on associations between OC or HRT use and breast or endometrial cancer fosters controversy for several reasons: level I evidence from randomized clinical trials is lacking; the results of level II and III epidemiologic studies are inconsistent; and few of the published studies are sufficiently large to estimate precisely the relative risks (RR) of cancer associated with use of exogenous hormones.

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This article adopts the viewpoint of the prescriber who must address the clinical issues arising from potential adverse effects, notwithstanding limitations in the evidence from relevant epidemiologic studies and meta-analyses. The ensuing discussion begins with the effects of OCs and HRT on endometrial cancer, and then considers their effects on breast cancer. Finally, the number of endometrial and breast cancers that would occur by age 65 years with and without use of reproductive hormones during the perimenopausal period is estimated.

Endometrial cancer

Endometrial cancers typically are hormone-dependent neoplasms that arise as a consequence of unopposed estrogenic stimulation with inadequate exposure to progestin [12,13]. Estrogen increases cellular proliferation and induces the synthesis of estradiol receptors in the endometrium [14]. Progestins not only diminish both of these effects [14,15], but also increase the conversion of estradiol to estrone, which has a lower affinity for estrogen receptors [16]. Progestins also prevent or reverse endometrial hyperplasia associated with use of unopposed estrogen [17–19]. Plausible biologic mechanisms exist for potential effects on endometrial cancer from the exogenous hormones in OC and HRT preparations.

Epidemiology of endometrial cancer

The risk of developing endometrial cancer rises with increasing age. In a cohort of 100,000 women, 2 develop invasive disease by age 25, 47 by age 40, 218 by age 50, and 1513 by age 70. These cumulative incidence rates, which are based on data from 1995 to 1997 for US women of all races [20], refer specifically to cancers of the uterine corpus, most of which are endometrial carcinomas: adenocarcinomas, adenoacanthomas, and adenosquamous carcinomas. The risk for a cohort of nonhysterectomized women is about 10% higher by age 40 and about 50% higher by age 70 [21].

The estimated case-fatality rate (the number of deaths per annum divided by the number of newly diagnosed cases) for endometrial cancer in the United States in 2000 was 17.5%, calculated from the ratio of approximately 6500 expected deaths and 36,100 expected new cases of endometrial cancer [22]. Based on follow-up of patients through 1997, the 5-year survival relative to women of similar age is 89% for women 45 to 54 years of age and 86% for women 55 to 64 years of age [23].

Risk factors for endometrial cancer, aside from the association with age and residence in western countries, include early age at menarche, late age at menopause, obesity, chronic anovulation, and nulliparity, all of which share a background with use of unopposed endogenous or exogenous estrogen [5,6].

OC use and endometrial cancer

Oral contraceptive use is associated with a lower risk of endometrial cancer, which persists after use is discontinued. A meta-analysis of 11 studies involving

1660 women with invasive disease found a significant trend of decreasing risk of endometrial cancer with increasing duration of OC use: risk was reduced by 56%, 67%, and 72% with use of combined OCs for 4, 8, and 12 years, respectively (RR = 0.44, 0.33, 0.28; one-sided P for trend: < .0001). Many of the RR estimates on which the meta-analysis was based were adjusted for age, body mass, and parity [21]. With respect to discontinued use, data from six studies involving 1340 women with endometrial cancer suggest that the lowered risk of disease while on oral contraception begins to rise after stopping OC use, although 20 years later the risk in former users is still almost 50% below that in women who have never used OCs. The aforementioned studies also indicate that a residual protective effect from prior oral contraception continues after the menopause, when the risk of endometrial cancer is greatest, and two studies indicate that the lower risk of endometrial cancer is similar for its histologic subtypes: adenocarcinoma, adenocanthoma, and adenosquamous cancer [24,25].

Estrogen-progestin doses and formulations

The effect of different estrogen-progestin doses and formulations on endometrial cancer risk is somewhat uncertain, perhaps because the threshold doses of estrogen and progestin needed for contraceptive efficacy exceed the levels needed for protection from endometrial cancer. The OC formulations in use in the United States during the early 1980s had similar beneficial effects on endometrial cancer risk [24]. One study found a reduced risk of endometrial cancer before age 45 with either high or low estrogen:progestin potency ratio OCs [26]. In another study, risk of endometrial cancer was unaltered by short-term use of low progestin OCs, but use of either low or high progestin OCs for 5 or more years decreased endometrial cancer incidence by approximately 75% [27]. Additional studies involving large numbers of women taking current formulations are needed to estimate the effect of present-day dosages and progestin products on endometrial cancer risk.

HRT and endometrial cancer

Women using unopposed estrogen for replacement therapy (ERT) are at increased risk of endometrial cancer. The currently recommended formulation for women with a uterus, however, which is combined estrogen-progestin replacement therapy (HRT), can eliminate entirely the estrogen-associated risk.

Unopposed estrogens: ERT

Ever-use of ERT. The risk of endometrial cancer is increased 2.8-fold (95% CI, 2.6 to 3) in women who have ever used ERT. This result is based on 30 case-control studies and 7 cohort studies involving 2766 ERT-exposed women with invasive disease [9]. Differential diagnostic assessment of women using ERT does not account for their increased risk of endometrial cancer: in three studies that included gynecologic and other controls, the risk of endometrial cancer in

ERT users, as compared with nonusers, was twofold higher (95% CI, 1.5 to 2.6) using gynecologic controls and 2.5-fold higher (1.9 to 3.4) using hospital or community controls [28–30].

Duration of ERT use. Estimates of risk based on duration of ERT use are more relevant than those for ever-use, because duration-specific estimates take into account the varying lengths of exposure in individual women. Longer duration of use was associated with progressively higher RRs: 1.7, 3.4, 5.4, and 7.1 at 1, 4, 8, and 12 years, respectively (P value for trend $< .0001$) [9].

Discontinued ERT use. The ERT-associated risk of endometrial cancer diminishes on stopping therapy, but even 12 years after discontinued treatment it may be as high as 1.9-fold greater than that in nonusers, depending on duration of use. The RR associated with use discontinued for less than 5 years is 3.5 (95% CI, 3 to 4), and it is 2.5 (95% CI, 1.9 to 3.2) for use discontinued for 5 years or more [9].

Estrogen type and dose. The risk of endometrial cancer does not differ by the type of estrogen in ERT: as compared with nonusers, risk was increased threefold (95% CI, 2.5 to 3.7) in women using conjugated estrogens and 2.6-fold (95% CI, 2 to 3.4) in women using other estrogens, a difference that is neither clinically nor statistically significant ($P = .65$). Higher estrogen content is, however, associated in a dose-response manner with significantly greater RR: 3.2, 4, and 5 for preparations containing less than 0.625 mg of conjugated equine estrogens, 0.625 mg, and more than 0.625 mg, respectively [9].

Known prognostic factors. Women who have favorable clinical prognostic factors at diagnosis of endometrial cancer are more likely to have been estrogen users. Five studies have found that use of ERT is associated with earlier stage and lower grade, possibly because of increased surveillance among users, with consequent earlier detection of tumors [31–35]. Alternatively, tumors arising with estrogen use may be less aggressive: in two follow-up studies, which adjusted for age, stage, grade, and myometrial invasion, the overall risk of death from endometrial cancer was 4.8-fold higher in patients who had not used ERT as compared with patients who had (95% CI, 2.2 to 10.3) [36,37].

Combined estrogen-progestin HRT

Seven epidemiologic studies now show that adequate progestin use offsets the increased endometrial cancer risk associated with unopposed estrogen [3,38–43]. The duration of progestin exposure in each cycle is a key feature of this protection [41,44,45]. The average HRT-associated RR of endometrial cancer, as compared with nonusers, was 2 (95% CI, 1.6 to 2.6), 1.3 (95% CI, 1.1 to 1.5), and 0.9 (0.7 to 1.2) with use of progestin in each cycle for less than 10 days, 10 days or more but not continuously, and continuous progestin use, respectively. Fig. 1 displays a summary of studies in which RRs were estimated by the length

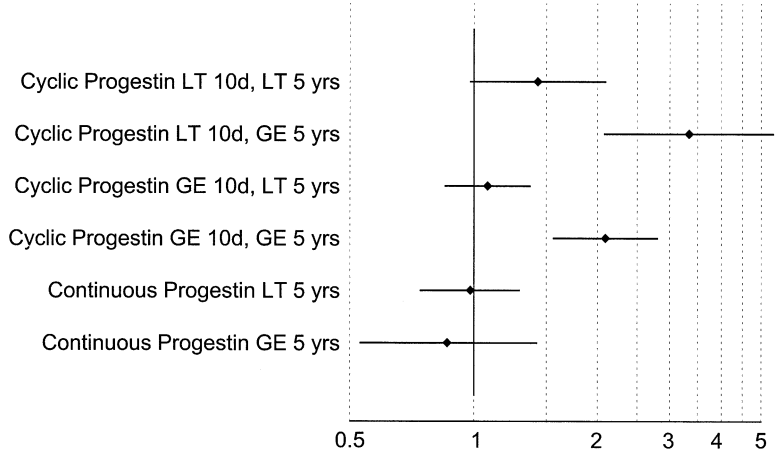

Fig. 1. Relative risk of endometrial cancer associated with combined estrogen-progestin hormone replacement therapy by duration of use and number of days of progestin per cycle. LT = less than; GE = greater or equal to; d = days; yrs = years; CI = confidence interval.

of progestin use in each cycle and by duration of use. With HRT use for less than 5 years, the risk of endometrial cancer was not significantly elevated above that in nonusers regardless of the duration of progestin exposure in each cycle, although a trend of declining risk with increasing progestin duration is suggested by the data. With more than 5 years' use of HRT, there was a significant trend toward lower endometrial cancer risk with longer progestin use in each cycle (P = .019). With continuous progestin exposure, regardless of the duration of use, the risk of endometrial cancer was similar to that in unexposed women. Although the data on combined estrogen-progestin HRT use are based on only 619 exposed cases, the evidence consistently indicates that use of progestins lessens the adverse effect of unopposed estrogen on the overall risk of endometrial cancer. Adverse effects from adding progestin would have to be very well proved to warrant a policy of prescribing unopposed estrogen for a long period to women with intact uteri.

Breast cancer

Breast cancers develop when cells undergo a series of mutations that cause damage to genes involved in the control of cell division [46]. The genetic damage inactivates repressor genes or activates proto-oncogenes, leading to structural changes and excessive proliferation. Estrogen and its metabolites may be related to initiation of breast cancer through oncogenic actions of the aromatase gene [47]. Promotion of breast cancer from estrogen and progesterone could arise by their accelerating the rate of breast epithelial cell division, thereby increasing the risk of a critical mutational change [48–50].

Epidemiology of breast cancer

Breast cancer incidence in the United States increased by approximately 4% per year during the 1980s, but in the 1990s the rate has stabilized at approximately 111 cases annually per 100,000 women [22]. As with endometrial cancer, the incidence of breast cancer rises with increasing age. In a cohort of 100,000 women, 8 develop invasive breast cancer by age 25, 443 by age 40, 1894 by age 50, and 7528 by age 70. These cumulative incidence rates are based on data from 1995 to 1997 for US women of all races [20].

The estimated case-fatality rate for breast cancer in the United States in 2000 was 22%, calculated from the ratio of approximately 40,800 expected deaths and 182,800 expected new cases of breast cancer among women [22]. The 5-year relative survival rates were 96% for localized breast cancer, 78% for cancer with regional spread, and 21% for cancer with distant metastases at diagnosis. Five-year survival does not reflect long-term prognosis, however, because survival after a diagnosis of breast cancer declines to 65% at 10 years and 58% at 15 years [51].

Major risk factors for breast cancer include increasing age, family history of breast cancer, atypical hyperplasia, nulliparity, and delaying childbirth beyond age 30 [52,53]. Other factors include early age at menarche, late age at menopause, higher education and socioeconomic status, and above-average alcohol consumption [1,4,54].

OC use and breast cancer

A reanalysis of epidemiologic data, published in 1996, addressed many of the common questions about breast cancer risk associated with OC use [7,55]. Since then further research has raised questions about how the effects of oral contraception may vary in women with a family history of breast cancer or genetic predisposition to the disease.

The Collaborative Group on Hormonal Factors in Breast Cancer reanalyzed data from 54 epidemiologic studies of breast cancer and OC use [7,55]. The database included a total of 53,297 women with breast cancer and 100,239 controls, most women being from North America or Europe. The main finding was a small increase in breast cancer risk during use of oral contraception, which began to decline shortly after stopping and which disappeared 10 years after discontinuation (Fig 2). The RR of breast cancer was estimated at 1.24 (95% CI, 1.15 to 1.33) for current users compared with nonusers. Ten or more years after stopping OC use, the corresponding RR was 1.01 (95% CI, 0.96 to 1.05). Notably, cancers in OC users were 12% less likely (95% CI, 5% to 19%) than those in nonusers to have spread beyond the breast.

The small increase in the likelihood of breast cancer in women using OCs represents a slightly higher risk at young ages, mostly less than 40 years, when women are taking OCs or have recently stopped, and breast cancer incidence is low. Fig. 3 shows estimates from the collaborative analysis for recent use of OCs (ie, current use or use that had been discontinued for less than 5 years). The RR of breast cancer for recent users who first began oral contraception before 20 years

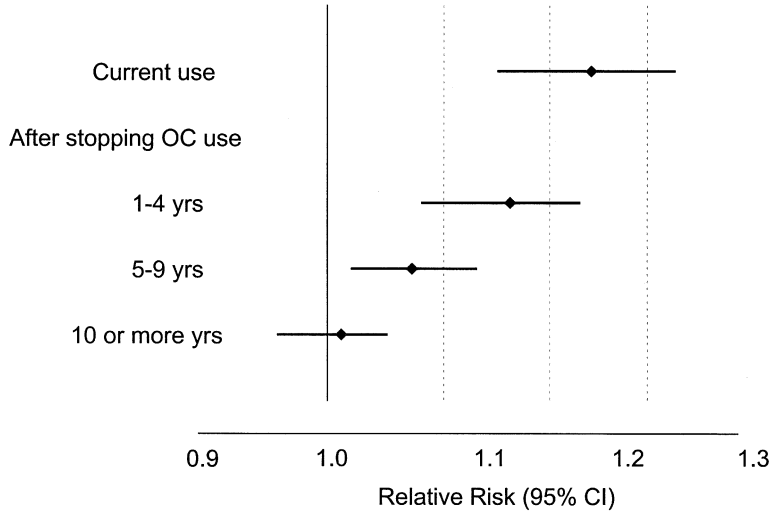

Fig. 2. Relative risk of breast cancer associated with oral contraceptive use. Yrs = years.

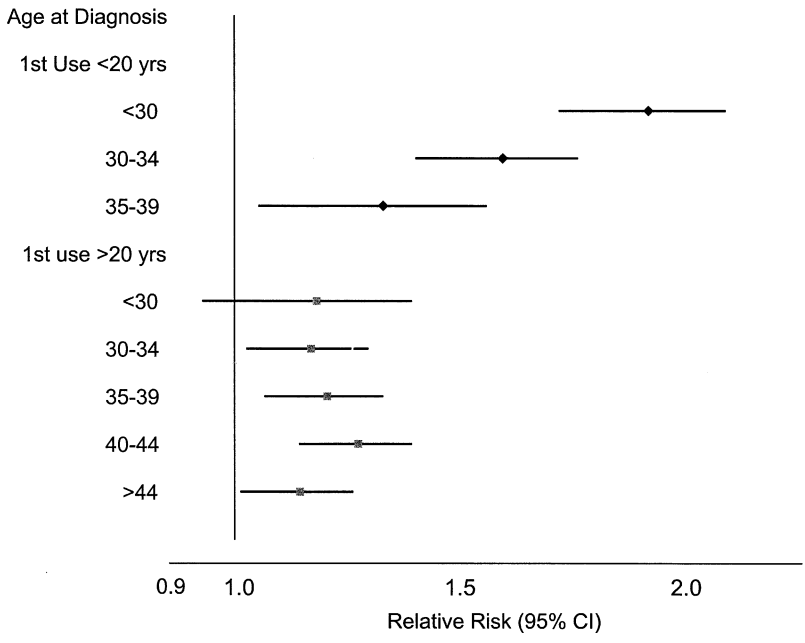

Fig. 3. Relative risk of breast cancer associated with oral contraceptive use by age at first use and age at diagnosis. Yrs = years.

of age, as compared with nonusers, was 1.95 for women less than age 30. The corresponding estimates of RR for women age 30 to 34 and 35 to 39 years were 1.54 and 1.27, respectively (trend: $P = .02$). For recent users who had initiated oral contraception after the age of 20, the RR of breast cancer was estimated to be 1.22 at 40 to 44 years and 1.11 at 45 to 49 years [7].

Absolute risk of breast cancer

A relatively small proportion of the expected lifetime incidence of breast cancer occurs before the age of 50 years, beyond which the effects of OC use have virtually disappeared. The preceding results indicate that the number of breast cancers attributable to OC use by young women is relatively small: 1.5 cases (95% CI, 0.7 to 2.3) and 4.7 cases (95% CI, 2.7 to 6.7) per 10,000 women using OCs from age 20 to 24 and 25 to 29, respectively, during and 10 years after discontinuation [7]. For women initiating use of OCs at age 40 and continuing for 5 years, the additional number of breast cancers were estimated at 32 (95% CI, 22 to 42) per 10,000 users [7].

Family history of breast cancer and OC-associated breast cancer risk

An important clinical question is whether any OC-associated breast cancer risk is amplified or attenuated in women with a family history of breast cancer. From results of the Collaborative Study, the answer is "no," but this reply needs to be tempered by more recently published findings [56]. For current or recent use (less than 5 years since discontinuation of OCs) compared with never use, the RR of breast cancer did not differ by family history status in the Collaborative Study: the estimates were 1.06 (95% CI, 0.76 to 1.36) for family history–positive women and 1.21 (95% CI, 1.14 to 1.28) for family history–negative women. Estimates of RR according to last use of OCs 5 to 9 years and 10 or more years in the past were close to 1, and were similar for women with and without a family history of breast cancer [7].

A recently published retrospective cohort study, which followed the relatives and descendants of patients with breast cancer, reported that ever-use of OCs (largely before 1975) by the sisters and daughters of the breast cancer patients was associated with an increased RR of breast cancer (RR = 3.3; 95% CI, 1.6 to 6.7). The RR of breast cancer the OC-using granddaughters and nieces was 1.2 (95% CI, 0.8 to 2), which did not differ from that in OC-using women who had married into the families with breast cancer (RR = 1.2; 95% CI, 0.8 to 1.9). The increased risk of breast cancer in the OC-using sisters and daughters of the breast cancer patients was chiefly caused by a RR of 11.4 observed when sisters and daughters had five or more blood relatives with breast or ovarian cancer, a situation occurring in 35 families of the 462 studied [56].

HRT and breast cancer

Hormone replacement therapy is most often prescribed in the fifth or sixth decade, when the incidence of breast cancer is increasing from approximately 100

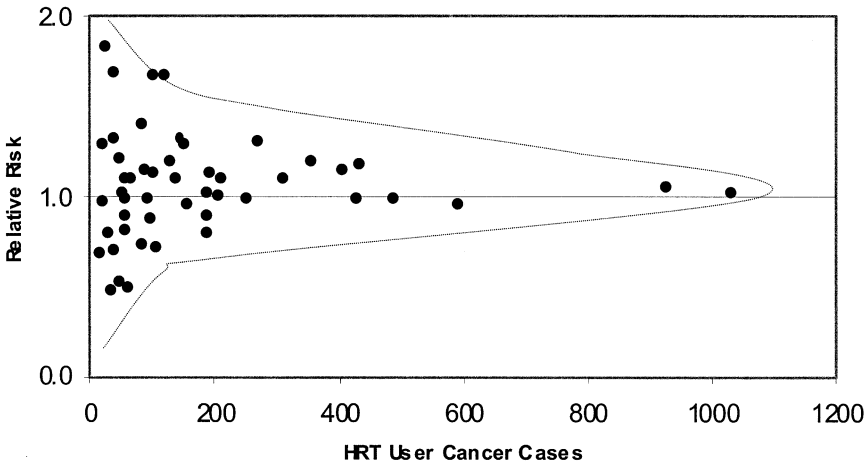

Fig. 4. Relative risk of breast cancer associated with hormone replacement therapy according to study sample size

cases to nearly 200 cases per 100,000 women per year [11]. Numerous observational studies have evaluated a possible association between HRT and breast cancer, but the results are not consistent. Fig. 4 shows that much of the variability in the published estimates of HRT-associated breast cancer risk is associated with studies involving fewer than 200 HRT-exposed breast cancer cases. A reanalysis of data from 51 epidemiologic studies published in 1997 by the Collaborative Group included 53,865 postmenopausal women in the main analyses. Thirty-three percent of the women had used ERT or HRT, but most of the known use was unopposed estrogen. The authors were able to assess hormonal constituents in only 4640 women, of whom 537 (11.6%) used estrogen combined with progestin. With current and recent use of HRT and ERT, breast cancer risk was 1.023-fold higher per year of use (95% CI, 1.011 to 1.036), which is comparable with a 1.028-fold higher risk per year of delay in the onset of menopause. With regard to use of HRT, the risk of breast cancer is estimated to be increased by 12% (RR = 1.12) with 5 years of use; by 26% (RR = 1.26) with 10 years of use; and by 41% with 15 years of use [8]. Five years after discontinuing HRT, the effect on breast cancer risk was no longer evident (RR = 1.01, 95% CI, 0.88 to 1.14) [8].

Combined estrogen-progestin HRT

The Collaborative Group's reanalysis included 215 exposed breast cancer patients who were known to have taken combined estrogen-progestin HRT: their RR of breast cancer compared with nonusers was 1.35 (95% CI, 0.85 to 2.17). Three subsequent studies included 409 [57], 263 [58], and 425 [59] cases exposed to combined estrogen and progestin. In a Swedish study, breast cancer risk remained elevated long after discontinuing use of HRT, and was higher with

testosterone-derived progestins but not progesterone-derived progestins [57]. An American follow-up study reported that the per annum breast cancer risk was 1.01-fold higher (95% CI, 1.002 to 1.03) with estrogen alone and 1.08-fold higher (95% CI, 1.02 to 1.06) with combined estrogen-progestin, compared with nonuse. Progestin use for 15 days or more per month was reported by only 12 cases, indicating that this estimate for combined estrogen-progestin mainly reflects cyclic use of progestin [58]. An American case-control study reported that the RR for 5 years' use of cyclic combined estrogen-progestin was higher than that for continuous combined estrogen-progestin: 1.38 (95% CI, 1.13 to 1.68) and 1.09 (95% CI, 0.88 to 1.35), respectively, compared with nonuse [59]. The authors estimate that the average per annum percent increases in breast cancer risk with use of unopposed estrogen, cyclic estrogen-progestin, and continuous estrogen-progestin, respectively, are 1.2% (95% CI, 0.1% to 2.3%), 7.8% (95% CI, 3.5% to 12.1%), and 1.8% (95% CI, 0.2% to 7%), compared with nonuse. These estimates are based on the two American studies, which included data for all types of progestins, and exclude the Swedish study because it reported separate estimates of risk for cyclic and continuous progestin use only for testosterone-derived progestins.

Family history of breast cancer

Women with a family history of breast cancer in close relatives are at increased risk of developing the disease. Surprisingly, the Collaborative Group's findings suggest that use of HRT, even long term, does not increase the risk of breast cancer in women with a positive family history. The RR of breast cancer in family history–positive women who had used HRT for 5 or more years, as compared with never-users, was 1.06 (SE = 0.2) for current or recent use (within 5 years of discontinuation) [8]. Results from a subsequent cohort study also suggest that use of HRT does not increase the risk of breast cancer in family history–positive women [60]. When the estimates of RR from the two preceding studies are combined, the RR of breast cancer associated with 5 years or more of current or recent use of HRT was 1.13 (95% CI, 0.82 to 1.57) for women with a positive family history of breast cancer, and 1.32 (95% CI, 1.20 to 1.46) for women with a negative family history [8,60].

Impact of reproductive hormone use during the perimenopause

The impact on breast cancer and endometrial cancer from use of reproductive hormones during the perimenopause centers on women age 40 to 49 and events during and after this period of time. For this purpose, the authors computed from available meta-analyses and individual epidemiologic studies estimates of the number of OC-attributable and HRT-attributable cancers. Where necessary, they computed summary estimates of RR by taking a weighted average of the log RRs reported from individual studies, with weights inversely proportional to variance. Large studies offering more precise estimates were given greater weight [10].

Table 1
Effect of reproductive hormone use on endometrial cancer and breast cancer: number of cancers arising from age 40 to 65 in 10,000 women who are cancer-free at age 40

	No hormone use	Excess (fewer) cancers with hormone use for 5 or 10 years	
Effect of Oral Contraception		*Age 40–44 y*	*Age 40–49 y*
Endometrial cancer			
No use of hormone replacement therapy	125		
Combined oral contraceptive use		(28)	(61)
Breast Cancer			
No use of hormone replacement therapy	638		
Combined oral contraceptive use		41	45
Effect of Hormone Replacement Therapy		*Age 45–49 yr*	*Age 40–49 yr*
Endometrial cancer			
No use of hormone replacement therapy	125		
Unopposed estrogen		194	373
Estrogen and cyclic progestin < 10 days per cycle		116	170
Estrogen and cyclic progestin ≥ 10 days per cycle		48	76
Estrogen and continuous progestin		(10)	(12)
Breast Cancer			
No use of hormone replacement therapy	638		
Unopposed Estrogen		66	101
Estrogen and cyclic progestin		97	206
Estrogen and continuous progestin		4	84

Using age-specific cancer incidence rates in US women (all races) for 1993 to 1997 [23,53], Table 1 shows the total number of cancers expected to arise from age 40 through age 65 (inclusive) in 10,000 women who are free of cancer at age 40, under the assumption that these women do not die from competing causes, such as cardiovascular disease. The table also shows estimates of the excess (deficit) number of cancers arising in 10,000 women using reproductive hormones. Calculations for endometrial cancer in relation to OC use are based on a recent meta-analysis [10], and those for breast cancer are based on the Collaborative Group's analysis [7]. Use of OCs in the model is assumed to begin at age 40 and continue for either 5 or 10 years. Estimates for HRT are given for unopposed estrogen, estrogen with cyclic progestin, and estrogen with continuous progestin. Use of ERT or HRT is assumed to begin at age 40 and continue for 10 years, or begin at age 45 and continue for 5 years. Calculations for HRT and endometrial cancer are from a published meta-analysis, combined with data from a more recent study [9,38]. The effect of ERT or HRT use on breast cancer is based on the collaborative study and two more recent studies [8,58,59].

With perimenopausal OC use for 5 years, there are 28 fewer endometrial cancers in 10,000 women as compared with the 125 cases expected (approximately 20% decreased), and there are 61 fewer cases (approximately 50% decreased) with 10 years of OC use. With 5 and 10 years of perimenopausal OC use, there are 41 and 45 additional breast cancers, respectively, which represents an approximate 6% to 7% increase over the 638 breast cancers expected to arise in 10,000 women who do not use OCs. Short-term perimenopausal use of OCs is estimated to increase slightly the total number of breast and endometrial cancers, whereas longer-term use results in a small net reduction. Such changes in net incidence are within the limits of error of the authors' methods for estimating risk.

Unopposed estrogen has the potential for a relatively large effect on cancer incidence. With perimenopausal ERT for 10 years, there are 373 additional endometrial cancers arising through age 65, giving a total four times the expected 125 cases in 10,000 women. Longer exposure to progestin in each cycle, however, progressively reduces endometrial cancer incidence. If estrogen and continuous progestin HRT are used in the perimenopause for 5 or 10 years, then the increased number of endometrial cancers associated with unopposed estrogen is eliminated: the expected number of cases arising from age 40 through age 65 is slightly less (10 to 12 fewer cases) than the 125 expected in 10,000 women not on HRT.

The number of breast cancers attributable to perimenopausal use of ERT for 5 or 10 years is 66 and 101, respectively, representing an approximate 10% to 16% increase over the expected 638 cases in nonusers. Use of cyclic progestin for 5 years leads to an additional 31 cases (97 total), representing a 15% increase over the expected 638 cases of breast cancer. With use of cyclic progestin for 10 years, there are 206 additional cases of breast cancer, a 32% increase over the expected number. For women using estrogen and continuous progestin HRT, however, only four additional cases of breast cancer arise from 5 years of use by 10,000 women; an estimated 84 additional cases (13% increase over expected) arise from 10 years of use.

The total number of breast and endometrial cancers arising from 5 years' use of HRT with estrogen and continuous progestin is virtually identical to the number arising in the absence of HRT, whereas a small net increase is estimated to occur with 10 years' use: 72 additional cases, representing a 9% excess over the 763 cases expected.

Summary

The effect of reproductive hormone use in the form of oral contraception or HRT on endometrial cancer incidence is not caused by simply bias: the epidemiologic studies are consistent; the effect of ERT is large; the biologic rationale cited is a plausible mechanism; and the response to progestin in oral contraception or combined HRT tends to confirm the biologic mechanism. In contrast, it remains unclear whether changes in breast cancer incidence following

use of oral contraception and HRT are caused by hormone exposure or to other factors: the results of epidemiologic studies are not entirely consistent, and the smaller relative effect on risk of breast cancer is susceptible to bias and other sources of error. Although the exact nature of the association between reproductive hormone use and breast cancer incidence is not yet clear, breast cancer is a common neoplasm in older women. Prescribers and users should take this into account in weighing benefits to ensure that unnecessary risks are avoided.

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Reproductive hormones and cancer Ovarian and colon cancer

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Ovarian and colon cancer have both been evaluated relative to whether or not exogenous reproductive hormone use affects the risk of these cancers in women. Studies specifically focusing on perimenopausal women do not exist. This article explores whether or not it is appropriate to make inferences to this population from other data. If one examines available statistics from the National Center for Heath Statistics, as a cause of death for women age 40 to 59 years in the United States, cancer is the overall leading cause followed by heart disease and accidents as somewhat distant numbers two and three [1]. Of the cancer deaths in this same age group, colorectal is the third most common cause with ovarian cancer the fifth most frequent cause [1].

Oral contraceptives and ovarian cancer

Although relatively uncommon compared with other cancers affecting women, ovarian cancer is the most common fatal malignancy of the reproductive tract in women [1]. In 2000, whereas about 23,100 new cases were diagnosed in the United States, in the same year approximately 14,000 women died from the disorder. Overall, it is the sixth most common cancer and the fifth leading cause of cancer death among US women [1]. There is no proven method for early detection, such that only about one fourth of the women have localized disease at the time of diagnosis. Five-year survival rates range from 46% among blacks to 50% among white women [1]. Risk factors for the disorder include age; nulliparity; family history of ovarian cancer (particularly first-degree relatives); and carriage of the *BRCA1* or *BRCA2* gene mutation [1–3]. These gene mutations

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are significant because the lifetime ovarian cancer risk for women with the *BRCA1* mutation is 44% [4], whereas the lifetime risk for women carrying the *BRCA2* mutation is 27% [5]. In contrast, for US women overall, the lifetime risk is about 1.8% [3].

Although 12 published studies in the decade of 1977 to 1987 suggested the possible protective effect of oral contraceptives against ovarian cancer [6–17], the analysis by investigators from the Cancer and Steroid Hormones study in 1987 was the first to report that ever-users of oral contraceptives had a substantial reduction in their future risk of ovarian cancer [18]. This large case-control study included 546 women with ovarian cancer who were enrolled from 1980 to 1982 between the ages of 20 and 54 years from eight population-based cancer registries in the United States. The control population consisted of 4228 women in the same age range identified through a random digit dialing method. The major finding was that ever-users of oral contraceptives had a relative risk of epithelial ovarian cancer of 0.6 (95% confidence interval, 0.5 to 0.7), a 40% reduction in risk. The protective effect was seen in women who had used oral contraceptives for only 3 to 6 months (relative risk 0.6, 95% confidence interval, 0.4 to 0.9) and continued for at least 15 years after use was discontinued. Type of oral contraceptive used did not affect protection. In particular, preparations with ethinyl estradiol doses as low as 35 μg showed protective effects. There were no substantial differences according to histologic type of epithelial ovarian cancer; there were too few nonepithelial ovarian cancer cases to assess risk adequately for these tumor types.

Over the past 25 years, at least 23 case-control studies [3,6–9,11–16,18–29] and three cohort studies [10,17,30] have examined the relationship between oral contraceptive use and ovarian cancer. Twenty-four studies confirm the protective effect of oral contraceptives, one study showed no effect [27], and one study showed a small increase in risk that was not statistically significant [23]. There seems to be between a 40% and 80% overall decrease in risk of ovarian cancer among oral contraceptive users. The protection begins about 1 year after initiating use and conveys about a 10% to 12% decrease in risk for each year of use. In addition, persistence of protection lasts between 15 and 20 years after discontinued use of oral contraceptives. This protective effect primarily involves epithelial tumors of the ovary. At least three studies [13,20,25] including one recent case-control study [25] involving 450 women with new epithelial ovarian cancer detected between 1989 and 1992 compared with 564 randomly selected population control in southern Ontario, Canada, indicate that the protection from oral contraceptives does not apply to mucinous ovarian tumors.

There are data to suggest that oral contraceptive use also reduces the risk of ovarian cancer among women who are at high risk for the disease. For example, one pair of investigators used data from the Cancer and Steroid Hormones study, data from the population-based cancer registries in the Surveillance, Epidemiology, and End Results network, and other studies to examine risk according to different age ranges [31]. In particular, they specifically evaluated the risk among nulliparous versus multiparous women and women with a positive family history

of ovarian cancer versus women with a negative family history. They concluded that use of oral contraceptives by nulliparous women for 5 years reduced their risk of ovarian cancer to that experienced by parous women who had never used this form of contraception. Similarly, oral contraceptive use for 10 years reduced the risk of ovarian cancer among women with a family history of the disorder below that experienced by never-users of oral contraception without such a family history. Data from one study also suggest that oral contraceptive use may protect women carrying the *BRCA1* or *BRCA2* mutation [3]. In this case-control study, 207 women with hereditary cancer were identified as cases and were compared with 161 of their sisters as the control group. All of the members of the case group carried either the *BRCA1* mutation (179 women) or the *BRCA2* mutation (28 women). Among the control women, 50 carried the *BRCA1* mutation, three the *BRCA2* mutation, 42 were known to be noncarriers of a *BRCA* mutation, and 66 had not been tested. The odds ratio for ovarian cancer among carriers of the *BRCA1* mutation for oral contraceptive users compared with nonusers was 0.5 (95% confidence interval, 0.3 to 0.9). Among the women carrying the *BRCA2* mutation, oral contraceptive users had an odds ratio for ovarian cancer of 0.4 (95% confidence interval, 0.2 to 1.1). The magnitude of the odds ratio estimates did not change when adjusted for possible confounders. This study is limited by its small sample size, however, particularly of the control group, the inclusion of oophorectomized women in the control group, and the inclusion of only living women in the case group. Relative to the latter point, if oral contraceptive use was associated with a higher case fatality rate for ovarian cancer, the present study would have exaggerated the estimate of the protective effect of oral contraceptives.

Using a different analytic approach, another group of investigators examined the risk of ovarian cancer associated with increasing parity and oral contraceptive use among carriers and noncarriers of the *BRCA1* and *BRCA2* mutation using a case-control study design [28]. They attempted to locate all epithelial cancers of the ovary among women of Jewish origin in Israel between March 1, 1994, and June 30, 1999. Controls were matched on age, birthplace, and residence on a two to one basis. Both the case and control populations were tested for the presence of *BRCA1* and *BRCA2* mutation. About 50% of the cases were excluded because of lack of pathology reports, inability to interview, refusal of testing, or inability to locate specimens. Of the original control sample, about 21% were tested for the mutations and were included in the analysis. Among the case group, 29% had either the *BRCA1* or *BRCA2* mutation, whereas only 1.7% of the control subjects had either mutation. Independent of mutation carriage, both increasing parity and duration of oral contraceptive use were associated with reduced risk of ovarian cancer. Among carriers of either mutation, however, only increasing parity but not increasing duration of oral contraceptive use showed a protective effect. The authors did note, however, that the low prevalence of oral contraceptive use and mutations in the control group limited the types of analyses that could be done. Although they recognized the need for further study of women with these risk factors, they did suggest caution in using oral contraceptives as chemoprevention

with such limited data because of the increased risk of breast cancer in women carrying these mutations.

The suggested mechanisms by which oral contraceptives may produce their protective effects include suppression of ovulation, reduction of gonadotropin levels, and induction of apoptosis [32–35]. There is some evidence that ovulation with injury to the capsule produces an inflammatory response with elevations of cytokines, prostaglandins, and leukotrienes [36]. It has been theorized that a decreased number of ovulations could reduce exposure of ovarian epithelium to certain types of cytokines that may play a role in the pathogenesis of ovarian cancer. The gonadotropin theory postulates that ovarian surface epithelium becomes entrapped forming an inclusion cyst as an initial step [37]. Malignant transformation then occurs under the influence of increased estrogen levels in the presence of persistently high gonadotropin levels, particularly luteinizing hormone. Because oral contraceptives suppress gonadotropins, there is a decreased likelihood of this transformation. The observed data, however, are not always consistent with these findings. For example, breast-feeding, which has been found to be protective against ovarian cancer, is associated with elevated follicle-stimulating hormone levels, a finding potentially in conflict with the gonadotropin theory [2]. Similarly, premature ovarian failure is associated with high gonadotropin levels, yet women with this condition do not seem to be at increased risk of ovarian cancer [2]. Animal studies that produce ovarian tumors under exposure to high levels of gonadotropins are often cited in support of this theory. The experimental tumors, however, are stromal not epithelial [37]. Oral contraceptives may also exert a direct effect on the surface epithelium of the ovary. One theory is that dysregulation of the normal apoptosis process to eliminate surface inclusion cysts may play a role in the formation of ovarian cancer. Data using a primate model indicate that oral contraceptives containing progestins may induce apoptosis of ovarian epithelial cells, a process that eliminates surface inclusion cysts [35].

It is important to recognize that most of the data supporting the protective effect of oral contraceptives are derived substantially from studies involving oral contraceptive preparations containing 50 μg of estrogen or greater and higher doses of progestin than that contained in current formulations. Although more recent studies have attempted to examine this issue, most have lacked sample sizes adequate enough to evaluate this issue [38]. A recent population-based case-control study, however, was able to ascertain risk of ovarian cancer according to estrogen and progestin dose [26]. Case subjects consisted of 767 women age 20 to 69 years with epithelial ovarian cancer diagnosed between May 1994 and July 1999. The cases were compared with 1367 community-based controls. After adjustment for current age, race, number of pregnancies, and family history, use of low-dose estrogen and low-dose progestin oral contraceptives resulted in a 50% reduction in risk (relative risk 0.5, 95% confidence interval, 0.3 to 0.6). This risk reduction was identical to that achieved by high-dose estrogen and high-dose progestin preparations (relative risk 0.5, 95% confidence interval, 0.3 to 0.7). It seems that these mechanisms are operant among current low-dose preparations.

It is unclear whether women using oral contraceptives for the first time in the perimenopause accrue the same benefit as other women. If one accepts that the major mechanism for protection relates to reduction in ovulation, then it is unlikely that perimenopausal women benefit as much as women who initiate oral contraceptive use earlier. If one accepts the apoptosis theory as being the most important, however, perhaps perimenopausal women have a similar degree of benefit as other women.

Hormone replacement therapy and ovarian cancer

The role of hormone replacement therapy in influencing risk of epithelial ovarian cancer is unclear at this point. Several groups of investigators have completed meta-analyses on this topic with somewhat conflicting results [2,39–41]. A pooled analysis of 12 case-control studies published between 1956 and 1986 did not show an increased risk of epithelial ovarian cancer among women exposed to noncontraceptive reproductive hormones beyond the age of 40 years of age [2]. This analysis included over 1200 cases and 5000 controls. All calculated relative risk estimates were around 1, although there was a trend suggesting a slight increased risk associated with more than 10 years use of hormone replacement therapy (relative risk 1.45, 95% confidence interval 0.91 to 2.29). It should be noted that because of the time frame of the studies, the replacement therapy was confined to unopposed estrogen. Garg et al [39] identified 327 citations in the English-language literature from June 1966 to June 1997 dealing with this topic. Eleven articles representing 12 analyses of 21 individual observational studies were included in the meta-analysis because they met the criteria of cases being age-matched to controls or the results age-adjusted and because they excluded women who had previously undergone bilateral oophorectomy. They concluded that ever-use of hormone replacement therapy was associated with an increased risk of invasive epithelial ovarian cancer (relative risk 1.15, 95% confidence interval 1.05 to 1.27). It is unclear what clinical significance can be attached to this finding given the modest increase in risk. Further, with a point estimate so close to 1, even small biases in the analyzed studies could negate the conclusion of an increase in risk associated with hormone replacement therapy. In addition, they also demonstrated a trend toward an increased risk with 10 or more years of use (relative risk 1.27, 95% confidence interval 1 to 1.61). The authors did state that their calculations for ever-use and duration of use showed evidence of heterogeneity.

Coughlin et al [41] suggested that the use of a fixed effects model in this meta-analysis was not appropriate given the evidence of heterogeneity. It is not clear, however, what effect there is on the point estimates if a different model is used for this same data set. As with the previous meta-analysis, particularly because many of the same studies were included in the analysis, most replacement therapy was confined to estrogen-only use. The meta-analysis of Coughlin et al [41] involved 15 case-control studies of estrogen replacement therapy and ovarian cancer

published between January 1966 and March 1998. Because the studies showed heterogeneity during the initial fixed effects analysis, a random effects model was used for further analyses. Using this approach they were unable to demonstrate a relationship between estrogen replacement and ovarian cancer (relative risk 1.1, 95% confidence interval 0.9 to 1.3). Further, they were unable to show any clear evidence of a dose-response or duration effect in the studies that had data on this topic. When they identified a relatively homogeneous subset of studies based in the United States, which used community controls, a trend toward a modest increase in risk was shown (relative risk 1.3, 95% confidence interval 1 to 1.6). This group suggested caution in interpreting any of their results because of the difficulty of controlling for potential bias or confounding.

Finally, Negri et al [40] have also reanalyzed four European case-control studies on this topic. The combined data set from two studies in Greece and one each in Italy and the United Kingdom included 1470 cases of confirmed epithelial ovarian cancer and 3271 control subjects. Ever-use of hormone replacement therapy compared with never-use resulted in an increased risk of epithelial ovarian cancer (relative risk 1.71, 95% confidence interval 1.30 to 2.25). There was a weak trend toward increased risk with duration of use when the investigators analyzed data from the two studies that had information on various aspects of replacement therapy use. Further, there was also a suggestion that the excess relative risk declined with time since last use. These findings seem compatible with a possible promotional effect of hormone replacement therapy on ovarian cancer growth. Further, this association may be related primarily to the estrogen component because, based on the publication dates of the four case-control studies, it is likely that a high percentage of the hormone replacement users were using estrogen alone. The authors also suggest caution regarding overinterpreting their findings. They suggest chance may play a role in the findings because hormone replacement therapy is more frequently prescribed in Europe to symptomatic perimenopausal women, a group that may have alterations in gonadotropin or steroid hormone levels that could place them at increased risk for ovarian cancer.

One large cohort study involving approximately 211,581 postmenopausal women in the United States and Puerto Rico has also suggested that estrogen replacement therapy is associated with an increased risk of ovarian cancer mortality [42]. Women were followed starting in 1982 for 14 years. During this time interval, there were 944 recorded ovarian cancer deaths. For women using estrogen replacement therapy at baseline (1982), the risk of subsequently dying from ovarian cancer was increased (relative risk 1.51, 95% confidence interval 1.16 to 1.96). Further, with duration of use for 10 or more years, both users at baseline and former users had an increased risk of ovarian cancer mortality (relative risk 2.20, 95% confidence interval 1.53 to 3.17, and relative risk 1.59, 95% confidence interval 1.13 to 2.25, respectively). Weaknesses of this study include exclusion of about 69% of women from the original cohort to form the study cohort, assessment of exposure through a self-administered questionnaire only at baseline, and use of death certificate data without verification. Also,

because of the study's timing, it is likely to reflect primarily estrogen replacement therapy without progestin use. In summary, studies evaluating the relationship between hormone replacement therapy and ovarian cancer are conflicting. Because calculated point estimates are either around 1 or only slightly elevated, unrecognized bias or confounders may be influencing these results. Given the timing of most of this literature, it also seems that if an association exists, it only involves the estrogen component of hormone replacement therapy. This certainly fits with the apoptosis theory of protection in that estrogen combined with progestin produced more that 20 times the amount of apoptosis in the ovaries of study animals than did estrogen alone [35]. Given these findings, it seems likely that perimenopausal women do not face an increased likelihood of ovarian cancer with hormone replacement use. Additional studies are needed, however, to examine fully this issue.

Oral contraceptives and colon cancer

Colorectal cancer is the third most common cancer in US women after breast and lung cancer. In 2000, there were an estimated 50,400 new cases of colon cancer and 16,200 cases of rectal cancer diagnosed; approximately 24,600 and 3900 women died from these two disorders, respectively [1]. Overall, the incidence of colorectal cancer is slightly higher in women than men, although rectal cancer is somewhat higher in men. Risk factors include age; cigarette smoking; first-degree relatives with colorectal cancer; and history of long-standing colitis, familial polyposis, or Gardner's syndrome [43,44]. Diets with reduced animal protein and supplementation with aspirin, nonsteroidal anti-inflammatory agents, folate, or calcium may reduce the risk of colorectal cancer for some patients [43]. Unlike ovarian cancer, there is ability to screen through rectal examinations, examining stool for occult blood, and endoscopy. It is unclear, however, what percentage of women at risk, particularly in the perimenopausal age range, actually undergoes the currently recommended screening procedures.

Five case-control [45–49] and two cohort studies [50,51] have evaluated the relationship between oral contraceptives and colorectal cancer, with four of the studies showing either a protective effect or a trend toward protection and three showing no effect or a possible increased risk for rectal cancer but not colon cancer. Potter and McMichael [46] conducted a community-based case-control study involving 99 colon cancer cases and 56 rectal cancer cases collected in South Australia between 1979 and 1980 compared with 311 control women age-matched at a two to one ratio. A major finding, determined through use of a conditional matched multiple logistic risk function model, was that parous women using oral contraceptives for over 2 years had a reduced risk of colon cancer but not rectal cancer (relative risk 0.16, 95% confidence interval 0.03 to 0.92). One weakness of the study, however, is that about 27% of potential cases and 30% of potential controls did not participate for a variety of reasons. In

addition, a number of subsets contained small numbers of subjects leading to wide confidence limits such that results need to be interpreted cautiously. Finally, given the time period of subject recruitment, it is unclear whether the findings apply to today's lower-dose preparations.

More recently, a large case-control study conducted in northern Italy between 1985 and 1992 recruited 709 cases of colorectal cancer and 992 control subjects from women hospitalized with nonneoplastic conditions [49]. Ever-use of oral contraceptives versus never-use through use of a multiple logistic regression was associated with a reduced risk of colorectal cancer (relative risk 0.58, 95% confidence interval 0.36 to 0.92). Further, there was a suggestion that duration of use (ie, more than 2 years) was associated with increased protection. Although this was a large case-control study, its findings also need to be interpreted with caution because the exposure to oral contraceptives among the case and control (4.2% and 9.3%, respectively) was limited.

A group of investigators from the Chicago metropolitan area collected 90 cases of large bowel cancer in women diagnosed between 1980 and 1983 and compared them with 208 control women recruited as spouses of large bowel cancer patients [47]. There was a suggestion that oral contraceptive use was associated with a reduced risk of large bowel cancer (relative risk 0.6, 95% confidence interval 0.28 to 1.34). Because there were only nine case subjects and 32 control subjects with a history of oral contraceptive use, the finding was not statistically significant.

More recently, the Nurses' Health Study cohort identified 502 cases of colorectal cancer among participants between 1980 and 1992 [51]. The study included over 1 million woman-years of follow-up for this subcohort of women with colorectal cancer. Hormone exposure before entry in the study and every 2 years was assessed along with other exposures. Among women using oral contraceptives, use for 6 years or greater was associated with a 40% reduction in risk of colorectal cancer (relative risk 0.60, 95% confidence interval 0.40 to 0.89). Further, the trend for the duration effect was statistically significant ($P = .02$). Given the timing of the study, it is unclear whether protection accrues to users of low-dose pills because this cohort primarily reflects use of high-dose oral contraceptives.

As discussed in the next section, there are potential explanations for a protective effect. Not all epidemiologic studies, however, have shown this protective effect. A study involving residents of the Seattle, Washington, area interviewed 143 women with large bowel cancer identified between 1976 and 1977 and compared them with a random sample of 707 control women selected through a household survey methodology [45]. Although a history of oral contraceptive use was more common among cases than controls suggesting a possible increase in risk for users, this difference was not statistically significant. Further, this finding was caused primarily by an association of oral contraceptive use with rectal cancer, albeit at a level that also did not achieve statistical significance. This study needs to be interpreted with caution because oral contraceptive use reflects only high-dose pills, because there were small numbers

of subjects in some of the analytic cells, and because of the inability to interview 38% of the originally identified cases.

The relationship between oral contraceptive use and colorectal cancer was also examined in 190 colorectal cancer cases and 200 age-matched control women derived from a population-based study of large bowel cancer conducted in Melbourne, Australia [48]. After adjustment for confounders including age, number of children, and age at first child's birth, an increased risk of rectal but not colon cancer was found among oral contraceptive users (relative risk 2.04, 95% confidence interval 1 to 4.14, $P = .04$). Further analysis of other possible risk factors indicated that rectal cancer risk was higher among oral contraceptive users who also drank beer (relative risk 6.96, 95% confidence interval 2.09 to 23.1, $P = .001$). Only 47 cases including 23 women with rectal cancer and 39 control subjects in this study, however, were past oral contraceptive users.

Finally, a prospective cohort of 35,215 women in Iowa, age 55 to 69 years, without a history of cancer at entry were evaluated for a variety of potential exposures including oral contraceptive use and the risk of colorectal cancer [50]. A questionnaire was completed in 1986 regarding the exposures; by 1990, 212 cases of colon cancer were documented among women in the cohort. After adjustment for potential confounders, no association was found between use of oral contraceptives and colon cancer. Although there are some data to suggest some type of association between exposure to oral contraceptives during the reproductive time span and colorectal cancer, clearly because of a variety of reasons, none can be termed conclusive. Further, there is no information that relates specifically to the perimenopausal woman.

Hormone replacement therapy and colon cancer

The relationship between colon cancer and hormone replacement therapy has received far more study than the relationship of this form of cancer to oral contraceptives. Over 30 studies and four meta-analyses have been completed [52–55]. The recent review of Crandall [56] and the meta-analyses of Grodstein et al [54] and Nanda et al [55] are used to highlight the current state of knowledge on this topic.

Crandall [56] reviewed English-language studies published through August 1999. A total of 35 studies, 3 meta-analyses, and 2 abstracts were examined. After elimination of interim results and abstracts, 30 studies were ultimately analyzed. Overall, 24 studies (15 case-control, 7 cohort, and 2 meta-analyses) showed protection; 11 studies showed no effect (five case-control, four cohort, one prospective trial, and one meta-analysis); and one case-control study demonstrated an increased risk with hormone replacement therapy. This last study included North American and Chinese women [57]. The Chinese women were recruited from a region with a high incidence of colon cancer and 90% of the hormone users had used hormones for 1 year or less. It is unclear whether hormone replacement therapy of this short duration is likely to have a causal

effect. Further, there may have been other factors related to diet or the environment that could have influenced the risk. With further analysis, Crandall [56] noted in her review that larger studies and studies published after 1995 seemed more likely to demonstrate a protective effect. Relative to type of hormone used, 25 studies did not distinguish between estrogen replacement therapy alone or in combination with a progestin. For the most part, among the few studies that did distinguish the type of replacement therapy, there was little difference in results between estrogen therapy alone and estrogen plus progestin therapy. Grodstein et al [54] also noted that most of the information provided by the studies in his meta-analysis involved estrogen replacement therapy. Of the three studies investigating estrogen and progestin combinations, however, one reported about a 40% reduction in risk with levonorgestrel being the predominant progestin [58], another a 45% reduction in risk [59], and the final study showing no association with either estrogen alone or in combination with a progestin [60]. Among the 17 studies that examined risk according to duration of use, only five studies showed a statistically significant decrease in risk with increasing duration of use. Finally, Crandall [56] noted that a high percentage of studies did not adequately control for potential confounders, such as diet, site of cancer, family history, or screening. Both of the recent meta-analyses calculated about a one-third reduction in risk of colon cancer among current or recent users of hormone replacement therapy, compared with about a 10% to 20% reduction among ever-users versus never-users of hormone replacement therapy. Although Nanda et al [55] determined that rectal cancer was not associated with hormone replacement therapy, Grodstein et al [54], on the basis of 10 analyzed studies, determined a reduction in risk for ever-users versus never-users (relative risk 0.81, 95% confidence interval 0.72 to 0.92).

Because adenomatous polyps precede colorectal cancers by a decade or more, any association between their presence and use of hormone replacement therapy is of obvious interest. Four studies have evaluated that relationship. Two case-control studies have determined a protective effect. Potter et al [61] in a study of 174 postmenopausal women with colorectal cancer compared with 289 women with normal colonoscopic examinations determined a reduced risk of polyps with 5 or more years of use (relative risk 0.43, 95% confidence interval 0.26 to 0.71). Peipins et al [62] also demonstrated about a 40% reduction in risk, whereas Jacobson et al [63] showed a trend toward reduced risk, which was not statistically significant. The prospective Nurses' Health Study reported a decreased risk of large adenomatous polyps for current users (relative risk 0.74, 95% confidence interval 0.55 to 0.99), whereas there was no association between small adenomatous polyps and hormone replacement therapy [64]. In summary, there is growing evidence from observational studies that current use of hormone replacement therapy protects against both colorectal cancer but also precursor adenomatous polyps. As is true with many observational studies, however, failure to control for potential confounders or bias requires that findings be interpreted with caution. Although one awaits well-designed randomized clinical trials to

confirm or refute the present findings, the results to date are clearly encouraging. Further, because much of the protection seems to benefit current users, one might anticipate that perimenopausal oral contraceptive users have benefits similar to other age groups.

Several mechanisms have been proposed to explain the protective effect of exogenous reproductive hormones on colorectal cancer. It has been suggested that bile acids either initiate or promote malignant change in colonic epithelium [65]. Because there is evidence that estrogen decreases bile acid secretion, this could protect the colonic mucosa [66]. Because bile acids are absorbed in the proximal bowel, there ought to be more protection against colon cancer rather than rectal cancer. As presented previously, the evidence does not seem to show a consistent differential effect. Estrogen receptors have been demonstrated in both normal and cancerous colorectal cells [67]. Although some studies have indicated that estrogen promotes growth of tumor cells [68], other studies suggest growth inhibition [69]. Others have noted an age-related reduced expression of the estrogen receptor gene and deregulated growth of colonic mucosa [67]. They suggest, based on their experiments, that estrogen accentuates growth suppression of neoplastic colonic cells perhaps through the estrogen receptor gene acting as a tumor suppressor. Another theory is that estrogen reduces insulin-like growth factor, which is a mitogen needed to allow both normal and cancerous cells to progress in the cell cycle [70]. Suppression theoretically reduces the risk of colorectal cancer growth.

Summary

Evidence continues to accumulate that oral contraceptive use provides substantial protection against ovarian cancer. Less clear is whether the benefit affects women with genetic predisposition or women in the perimenopausal age range. The role of hormone replacement therapy in the occurrence of ovarian cancer is unclear. Available evidence suggests that if there is any potential risk, it involves women who use estrogen alone. Few women if any entering the menopause are at risk. There is some evidence that oral contraceptives have a favorable impact on the risk of colorectal cancer. Available data are limited. Finally, there is growing evidence that hormone replacement therapy reduces risk of colorectal cancer, a benefit that accrues to perimenopausal women.

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Counseling the perimenopausal woman

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As we enter the twenty-first century, the numbers of perimenopausal (PMP) women are rapidly increasing in the United States, largely because Baby Boomers are entering this phase of their life. It has been estimated that there are 10 million women currently between the ages of 45 and 49 [1]. Although thousands of studies have been done evaluating menopausal women, there are few that evaluate the changes that occur in the transition from premenopause to postmenopause. This fact makes it more difficult for both the health care provider and the PMP woman to make well-informed decisions about health care and health maintenance. Until now, there has not been an agreed on definition of the perimenopause. Recently, the Council of Affiliated Menopause Societies defined the perimenopause as "the period immediately prior to the menopause (when the endocrinologic, biologic and clinical features of approaching menopause commence) and the first year after menopause," with natural menopause being defined as "the permanent cessation of menstruation resulting from the loss of ovarian follicular activity, natural menopause is recognized to have occurred after 12 consecutive months of amenorrhea, for which there is no other obvious pathologic or physiologic cause" [2,3].

Currently underway is the Study of Women's Health Across the Nation, which evaluates many aspects of the menopause and PMP transition in a multiracial, multi-ethnic, community-based sample of women. The women in this study are between the ages of 42 and 52 at enrollment and will be followed for several years through the transition to menopause. Until such time as this study is completed, clinicians are forced to rely on menopausal data or data from the studies done looking at this age group of women using oral contraceptives (OCs) [4].

Concerns of the PMP woman

One of the premises of caring for the PMP woman is that this is a normal phase in her reproductive life. Many women sail through this time with few, if

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any, symptoms. For those women, the annual examination (in the late 30s or early 40s) is an ideal time to begin to prepare them for what lies ahead. She may already have excellent health habits and few questions. This generally is not the type of patient who comes for assistance and most of this article deals with management of the symptomatic patient.

Menstrual cycle changes

One of the most common symptoms these women present with is a change in menstrual cycle. This is a time when the menses can become shorter, longer, heavier, lighter, closer together, or further apart, and all of this can be normal. Often reassuring women that, although it may not be their usual cycle, it does not mean there is anything pathologic, is a relief. Bleeding that is longer than 7 days, occurring less than 21 days (from day 1 of cycle to day 1 of next cycle), intermenstrual, or much heavier than usual leading to anemia does need evaluation. Some possible causes of abnormal bleeding include pregnancy, uterine myomas or polyps, blood dyscrasias, anovulation, endometrial hyperplasia, and cancer. If abnormal bleeding is present, it must be evaluated by any of several methods including history and physical examination, endometrial biopsy, vaginal probe ultrasound with saline infusion, or hysteroscopy dilation and curettage.

Weight

Weight gain is another common concern. Women tend to develop an increase of adipose tissue and decrease of muscle mass with aging. In a culture that values youth and slimness, this can be a distressing event. In their longitudinal study evaluating weight and the menopausal transition, Avis et al [4] found that the menopausal transition was not consistently associated with weight gain, nor was the use of hormone therapy. The two factors most associated with weight were alcohol consumption and exercise.

Vasomotor symptoms

Up to 85% of all PMP women have hot flashes or night sweats. Of those women who do have hot flashes, 10% persist throughout life unless treated. Vasomotor symptoms can last a few months or many years and can range from mild (no disruption of usual activity) to nearly debilitating. Many studies show that these symptoms are more severe with surgical menopause.

Premenstrual syndrome

Some PMP women experience mood changes, irritability, and changes in sexual function. Because many of these symptoms are also associated with premenstrual syndrome, they must be distinguished from each other. This is best done by having the patient keep a menstrual diary, because timing is important in differentiating between them, with symptoms being confined to the luteal phase

in premenstrual syndrome. Women who have been previously diagnosed with premenstrual syndrome may note increased symptoms in the perimenopause.

Insomnia and other sleep disturbances

Although the etiology of sleep disturbance in the PMP and beyond is not fully understood, it is clear that this is a major problem for women at this time. These disturbances can cause fatigue, inability to concentrate, and mood changes leading to a diminished quality of life. Although there is little evidence that estrogen can alleviate these symptoms in the PMP, there are data showing that hormone replacement therapy (HRT) does improve symptoms in the menopause. Other measures that can be taken include developing a bedtime routine; avoiding alcohol, caffeine, and spicy foods; keeping a cool environment; and other techniques used to combat insomnia.

Memory

Many women report a loss of memory, forgetfulness, or difficulty thinking beginning in the PMP. There are few studies done to evaluate this problem. With recent studies showing mixed evidence of the protective effect of estrogen on Alzheimer's disease, the possible effect of estrogen on memory is now being evaluated. As a part of the longitudinal Seattle Midlife Women's Health Study, a memory function questionnaire showed that age was not related to any indicators of memory except retrospective memory, in which younger women felt their memory now was worse as compared with the past. Although most women reported difficulty in remembering names at least some of the time, they did not rate the problem as serious [5]. This topic is dealt with in more detail elsewhere in this issue.

Changes in sexual function

The PMP time can herald a time of marked changes in various aspects of a woman's life including sexual function. Although most of the studies evaluating sexual function at this time are done by questionnaire, there are both objective retrospective and prospective studies showing that PMP women remain sexually active but less so. Sexual dysfunction in most populations studied in the United States is quite high, between 31% and 87% [6]. It is imperative that practitioners either be able to discuss their patients' sexual complaints or be able to refer them to appropriate sources. Questions about sexual function should be a routine part of annual examinations and asked at any other appropriate time. The most common sexual dysfunction in this author's practice is low libido, with nearly 50% of women having this symptom. Although the role of estrogen is clear in the maintenance of vaginal health in postmenopausal women, there are no data for its use in the PMP woman. The role of testosterone is even less clear because there are no data in its use in PMP women. Because libido is so complex, involving not only genital arousal, a woman's psychologic state, her expectations about the

Table 1
Perimenopausal health maintenance

- History
  - Family history
    - Cardiovascular disease
    - Cancer
    - Diabetes
    - Osteoporosis
    - Other (Alzheimer's disease, mental illness, obesity)
  - Personal history
    - Health status (including symptoms of menopause)
    - Dietary and nutritional assessment
    - Physical activity
    - Substance use and abuse
    - Abuse or family violence
    - Sexual practices
    - Mental attitude (depression, anxiety, stress)
    - Psychologic factors (marital status, work, family dynamics)
- Physical examination
  - Height
  - Weight
  - Blood pressure
  - Oral cavity
  - Neck: adenopathy and thyroid gland
  - Breasts and axillae
  - Abdomen
  - Pelvic and rectovaginal examination
  - Skin
- Laboratory tests
  - Pap test (physician discretion after three consecutive normal tests if patient is considered to be low risk)
  - Mammography (every 1–2 until age 50; yearly beginning at age 50)
  - Cholesterol (every 5 y)
  - Fecal occult blood test
  - Sigmoidoscopy (every 3–5 y after age 50)
  - Other tests (based on risk factors)
- Immunizations
  - Tetanus-diphtheria booster every 10 y
  - Influenza vaccine (yearly beginning at age 55)
  - Other (based on risk factors)
- Education and counselling
  - Sexuality
    - High-risk behaviors
    - Contraception options
    - Sexuality transmitted disease
    - Sexual function
  - Fitness
    - Hygiene (including dental care)
    - Diet and weight control
    - Exercise

(continued on next page)

Table 1 (*continued*)

Psychosocial
Family relationships
Domestic violence
Job or work satisfaction
Lifestyle and stress
Sleep disorders
Cardiovascular risk factors
Hypertension
Hyperlipidemia
Obesity/ or diabetes mellitus
Health and risk behaviors
Injury prevention
Breast self-examination
Exposure to ultraviolet rays
Suicide prevention
Substance abuse
Hormone therapy
Risks versus benefits
Side effects
Therapeutic regimens

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sexual encounter, the state of her relationship, and what is happening in her day-to-day life, a prescription for testosterone is rarely the entire solution. The practitioner can provide appropriate pharmacologic therapy, accurate information, and counseling (or appropriate referral) to help her maintain sexual health.

Health care maintenance

This can be a time when a woman reassesses her health and may be an excellent time to establish new healthy behaviors. The American College of Obstetrics and Gynecology has an excellent plan for health care maintenance in this time (Table 1). Osteoporosis, cancer, and complimentary medicines are dealt with elsewhere in this issue.

Attitudes of the PMP woman

Some women may experience the symptoms of PMP as trivial and merely an inconvenience, whereas others find that they are very disturbing. By definition, the PMP spans the possible ages of 35 to 60. When the symptoms begin in the late thirties or early forties, many women have not given a thought to menopause and are totally unprepared for this eventuality. In particular, a woman who begins to have hot flashes or other PMP symptoms before she has completed (or even

begun) her childbearing may be especially devastated. She may be frightened that something is desperately wrong or in denial that these symptoms could be heralding the oncoming menopause. On the other hand, a 55-year-old woman who first experiences these symptoms may welcome the end of menstruation. A clinician must be able to understand the context for either woman. Women and clinicians may have different definitions for menopause. Often for the woman, she is "menopausal" if she begins having symptoms, so it is important that both clinician and woman "be on the same page" for clarity to occur. Fogel and Woods [7] state that both socialization and anticipation of midlife by one's cohort influences how women interpret the events of the PMP. In a survey done by *New Woman* magazine, younger women were more fearful of aging. Fifty-four percent of women in their 20s were more fearful of growing old as compared with 23% of women over age 60 [8].

Because daughters are often the primary source of caring for aging parents, this can cause conflict with their other roles at midlife. It is often a time called the "sandwich generation." This author has had patients and friends who, indeed, could be called the "club sandwich generation," with responsibility for aging parents and grandparents and at the same time have their own children with grandchildren moving back into their homes. In studies, however, this dilemma was only infrequently a cause of conflict [9].

Physician and caregiver-patient interaction

When counseling the PMP woman, many things must be considered. The counseling must be patient centered. The critical nature of the medical interview in the clinician-patient relationship has been well established; it is the most important determinant of patient satisfaction and adherence to therapy [10]. Although many recent medical school graduates have been evaluated doing patient interviews, most physicians educated before 1990 have not been schooled in behaviors associated with the various structural elements of the interview. Table 2 may prove helpful to review the elements of the successful interview.

The caregiver as motivator

One of the most difficult challenges faced by clinicians is how to motivate women to make positive changes in their lifestyle, such as weight loss, exercise, and smoking cessation. It takes more than simple statements such as, "You need to lose some weight," "Smoking is bad for you," and so forth. Prochaska and DiClemente [9] have developed a model for behavior change that can be used in many situations. It is based on the assumption that patients must be ready to change behavior, that there are stages to this readiness, and that different interventions must be used at different stages. Sallis [9] describes the following stages:

Precontemplation: the patient is not even ready to think about behavior change, much less change the behavior

Table 2
Behaviors associated with the 14 structural elements of the interview

Preparing the environment
Create privacy
Eliminate noise and distractions
Provide comfortable seating at equal eye level
Provide access
Preparing oneself
Eliminate distractions and interruptions
Focus
Self-hypnosis
Meditation
Constructive imaging
Let intrusive thoughts pass through
Observation
Create a personal list of categories of observation
Practice in a variety of settings
Notice physical signs
Presentation
Affect
What is said and not said
Greeting
Create a personal stereotypic beginning
Introduce oneself
Check the patient's name and how it is said
Create a positive social setting
Introduction
Explain one's role and purpose
Check patient's expectations
Negotiate about differences in perspective
Be sure expectations are congruent with patient's
Detecting and overcoming barriers to communication
Develop personal list of barriers to look for
Include appropriate language
Physical impediments, such as deafness or delirium
Include cultural barriers
Recognize patient's psychologic barriers, such as shame, fear, and paranoia
Surveying problems
Develop personal methods of initiation of problem listing
Ask "what else" until problems are elicited
Negotiating a priority problem
Ask patient for priorities
State own priorities
Establish mutual interests
Reach agreement on order of addressing issues
Developing a narrative thread
Develop personal ways of asking patient to tell her story
Ask when last felt healthy
Ask about entire course of illness
Ask about recent episode or typical episode

(continued on next page)

Table 2 (*continued*)

Establishing the life context of the patient
Use first opportunity to inquire about personal and social details
Flush out developmental history
Learn about patient's support system
Learn about home, work, neighborhood, and safety
Establishing a safety net
Memorize complete review of systems
Review issues as appropriate to specific problem
Presenting findings and options
Be succinct
Ascertain patient's level of understanding and cognitive style
Ask patient to review and state understanding
Summarize and check
Tape record and give tape to patient
Ask patient's perspectives
Negotiating plans
Activate patient
Agree on what is feasible
Respect patient's choices whenever possible
Closing
Ask patient to review plans and arrangements
Clarify what to do in the interim
Schedule next encounter
Say goodbye

From Lipkin M, Frankel RM, Beckman HB, Charon R, Fein OG. Performing the interview. In: Lipkin M, Putnam SM, Lazare A, editors. The medical interview: clinical care, education, and research. New York: Springer-Verlag; 1995. p. 65–82; and Lipkin M. Physician-patient interaction in reproductive counseling. Obstet Gynecol 1996; 88: 31S–40S. Reprinted with permission from the American College of Obstetricians and Gynecologists.

Contemplation: the patient is thinking about the behavior change but not yet acting on it

Preparation: the patient is actually doing something about making a change, although it may not be consistent

Action: the patient is doing what needs to be done to acquire her goals and has been doing so for up to 6 months

Maintenance: the patient has been in action to attain her goals for longer than 6 months

Table 3 demonstrates the changes, the counseling goals, and strategies for the clinician.

Counseling strategies

Graziottin [11] has developed successful strategies in addressing women's concerns about the menopause and HRT and one may be able to adapt them to the use of OCs in the perimenopause. He states there are many reasons why women do not start hormone therapy or discontinue it, including a reluctance on the part

Table 3
Stages of motivational readiness

Stage	Characteristics	Counseling goals	Strategies
Precontemplation	Not ready to change (not yet taking or thinking about needed action)	Change thinking or motivate to contemplate change	Increase knowledge and motivation (identify personal benefits of change and risks of not changing)
Contemplation	Almost ready to change (contemplating needed action)	Establish commitment to change; encourage to move forward	Verify personal benefits; identify and address potential barriers
Preparation	Working on making change (talking or researching or taking needed action, but on inconsistent basis)	Provide with tools to make change ("how to's"); encourage to start making consistent changes	Encourage use of behavioral strategies (support, rewards, scheduling, and so forth); verify personal benefits; address obstacles
Action	Making change (meeting guideline requirements for up to 6 mo)	Provide reinforcement, encouragement, ongoing follow-up; prevent relapse	Return visits, phone calls, mailed material (clinician or ancillary staff), referral; praise accomplishments; reinforce benefits; address relapse (if needed)
Maintenance	Continuing to meet guideline requirements for 6 mo or longer	Provide reinforcement, encouragement, ongoing follow-up;prevent relapse	Return visits, phone calls, mailed material (clinician or ancillary staff), referral; praise accomplishments; reinforce benefits; address relapse (if needed)

From Prochaska JO, Redding CA, Evers KE. The transtheoretical model and stages of change. In: Glanz K, Lewis FM, Rimer BK, editors. Health behavior and health education, 2nd edition. San Francisco: Jossey-Bass; 1997. p. 60–84; with permission of Medquest Comm., LLC.

of the clinician to prescribe the therapy, in which case negative attitude toward treatment can be passed to the patient; the woman's own ambivalence toward HRT including the risks and benefits of HRT; and finally, the side effects that may ensue from beginning HRT.

Graziottin's [11] strategies include the following points. The clinician should be aware of personal attitudes about the therapy. To do this, one may need to re-examine attitudes and reassess the evidence and sort this out from personal subjective feelings. Listen to the patient's fears. By making her feel that she is an active member of a team and has a full understanding of the physiologic changes that are occurring she may be more likely to adhere to therapy. The clinician needs to know how each patient can best learn all of the information that she needs to be able to make an appropriate decision for herself. People have different ways of learning. Some learn by active participation, some by reading, some by viewing, and some by listening.

To illustrate this point, Freedman [12] describes the approach that he uses in counseling his PMP patients that has led to a 70% adherence rate for OCs and HRT for 3 years or longer. He discusses the noncontraceptive benefits, stressing that OC use reduces their risk of endometrial and ovarian cancer, setting the stage for discussing HRT in later years. He stresses that the use of OCs is only one component of a comprehensive wellness strategy to include adequate calcium intake, adequate exercise, appropriate nutrition, smoking cessation, limited if any alcohol consumption, and appropriate health care maintenance. In addition to personal interaction with his patients he holds a seminar on a quarterly basis at which time as many as 100 women attend a 45-minute lecture followed by a question-and-answer session. This gives attendees an opportunity to have their own questions answered and to interact with other women who are having the same experiences. He addresses directly their concerns about breast and ovarian cancer, osteoporosis, cardiovascular disease, bleeding, and nonpharmacologic interventions. He enters into a "contract" with his patients to talk freely and openly about all decisions affecting their health. He believes it is essential to acknowledge that if the patient decides against the use of OCs or HRT, it does not diminish the patient-physician relationship. The patient also agrees to call him before stopping therapy. He acknowledges that OCs and HRT are not for everyone. A critical piece to his practice is to see patients back within 3 months after initiating therapy if they are having any difficulties. If not, they can cancel their visit. The telephone line, however, must remain open and his practice employs full-time "telephone nurses" to answer any questions or concerns.

Graziottin [11] states that it is critical to take the PMP woman's concerns seriously. Although the term *nuisance* side effects has been used, the side effect may be more than a nuisance to her, could be a reason for discontinuing therapy, and it may belittle her by describing them as such.

Choosing a therapy

If the decision has been made to use a hormone therapy several things must be considered. By definition, women in the PMP may still be ovulating. As such, the use of HRT can be fraught with bleeding problems because most HRT regimens do not stop ovulation. A woman can bleed in response to her own irregular ovarian cycles and in response to a HRT regimen, and irregular bleeding is probably the reason most women discontinue HRT. If a woman is a nonsmoker and has no other contraindications for the BCP, it may be an excellent choice for her in the PMP.

Some women may be reluctant to use OCs and in these women it is important to ask important open-ended questions, such as "What good things do you know about OCs?" or "What has been your experience with OCs?" or "What is the worst thing you have heard about OCs?" This allows the clinician to reinforce patient knowledge or correct any misconceptions that she may have, and tailors the discussion to her unique perspective [13].

Risk discussion

When describing both the risks and benefits associated with OCs it is very important not to use epidemiologic jargon but to translate that into information that she can understand to help her make decisions. Most patients do not understand the terms *relative risk*, *absolute risk*, *attributable risk*, and so forth. When she hears on the evening news that a relative risk increases by 50%, it can sound frightening. A more useful tool in this instance may be a visual aid showing that a risk that increases from four per thousand to six per thousand is a 50% increased risk, which may not be so frightening. An essential tool is to keep an open telephone line. It is most helpful to have a nurse well trained in HRT-OC use to triage the calls. In many practices, including the author's, the nurse is able to manage 90% to 95% of these calls, referring only 5% to 10% to the physician.

Perhaps the major risk women attribute to OCs is the perceived increased risk of breast cancer. Patients should be informed that the current evidence, including the collaborative reanalysis of 54 studies, showed no overall effect of OCs on the risk of diagnosis of breast cancer, either by duration of use, formulation, age at first use, or family history of breast cancer. There was a slight increased risk in the diagnosis of breast cancer for current users of OCs; the OC-associated slight increased risk of diagnosis of breast cancer decreased rapidly after cessation of use, and within 10 years was eliminated all together. In addition, the breast cancers diagnosed in OC users were more likely to be localized to the breast, thereby being more easily treatable than the invasive cancers in nonusers. It is believed by many that the increased risk of diagnosis may be caused by detection bias (ie, women who are OC users have more frequent breast examinations and mammograms) [13].

Women may have questions about other safety issues, such as endometrial and ovarian cancer and cardiovascular disease. OC use has been found to decrease the risk of endometrial cancer by 50% compared with nonusers. In addition, OC use has been shown to reduce the risk of ovarian cancer by at least 40%. It is now known that the only women who are at risk for myocardial infarction are those who are over 35 years of age and smoke. It has been established for years that OCs carry a threefold to fourfold increased risk of venous thromboembolism [14]. Because the incidence is low, however, the overall risk is relatively small.

It is important to work with the patient to select the therapy (if any) that is best suited to her, creating and implementing an individualized action plan that has the fewest side effects and returns her sense of well-being. She needs to be very clear as to why she is beginning therapy, not just because "Well, you recommended it." In addition, she should understand that the decision to begin OCs or HRT is not carved in stone and can be changed at any time.

The clinician must have knowledge about the various estrogens, progestins, and androgens, and routes, doses, and combinations available. The noncontraceptive benefits of BCPs relative to the PMP woman should be stressed including relief of vasomotor symptoms, regulation of the menstrual cycle, protection against bone loss, improvement in acne, and relief of sleep disturbance [13].

An important component of perimenopausal counseling is anticipatory guidance to possible side effects of the BCPs that may occur, such as breakthrough bleeding; fluid retention; breast tenderness; nausea; weight gain (or perceived weight gain); and so forth. If she is forewarned about the symptoms and reassured that most of them resolve within a few weeks or months, she is more apt to remain on therapy. It is advisable that she be scheduled for a return appointment in 6 to 8 weeks so that therapy can be altered if necessary.

The most important aspect of good PMP counseling is effective communication. To ensure that this is occurring, the clinician needs to develop a good patient-practitioner relationship and have some knowledge about possible barriers to good counseling. The patient may be misinformed, have difficulty making decisions, be anxious, or may respond negatively to the style of the clinician. The clinician may have too little time to counsel his or her patients adequately, may be a poor listener and not solicit patient participation in the decision-making process, be considered unapproachable, or have a different health model. Only by establishing trust can a clinician provide optimal care for this patient.

Clinicians need to recognize if they have inadequate training in the PMP transition, and if so need to get the knowledge necessary to care for this patient population. In addition, they may have their own beliefs and stereotypes about PMP that may not fit the particular woman seeking their expertise.

Should a woman seek therapy for her symptoms, the responsibility of the clinician is to ensure she is well informed. This can rarely be done in one office visit. This author rarely writes a prescription for OCs or HRT on a first office visit. Rather, the patient's most effective way of learning is elicited and they return for an additional visit to answer all questions that arose during the educational process, be it video, reading, audio, discussion, and so forth.

The clinician needs to acknowledge that the patient has many sources of information (or misinformation), such as friends, relatives, and media, and the messages are often conflicting. She may have a general distrust of the pharmaceutical industry, underestimate the benefit, overestimate the risk, be concerned about expense, underestimate long-term benefits, and so forth. Unless one addresses these issues, that patient may be one of the 30% or so who never fill a prescription.

There are some patients who wish to participate fully in decision making, and others who do not want to be a partner in health decisions would rather "be taken care of." The clinician must be able to recognize the two types of patients.

There are several strategies one can use to ensure patient satisfaction with therapy. They include the following: going over the risks and benefits as they pertain to the patient; reviewing the options for her based on individual assessment of the patient; discussing possible length of therapy (depending on the reason for initiating it); giving samples (if one has the appropriate one for her); scheduling follow-up in 6 to 8 weeks; ensuring she has the nurse's telephone number if she has questions; and reassuring her that the clinician is available if any problems arise.

Summary

The PMP time is a time of hormonal fluctuations. As such, a woman may have many symptoms or none. It may also be a time of many life changes both positive and negative. The clinician has an opportunity to educate patients to prepare them for this time and to help them maintain health through the menopause. Because this time in a woman's life is largely unstudied, treatment options (if any) can be uncertain. For many women, the choice to use an OC to control cycles and treat other symptoms is an option. Finally, it is a time when excellent communication and counseling are imperative. The counseling must be effective and in a manner in which the patient learns well. The communication between the clinician and patient must be open and the patient must have realistic expectations about any therapy that may be chosen. The clinician must recognize that each woman is unique and has unique needs. A goal for both should be relief of symptoms, health maintenance, and enhancement of her overall quality of life.

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Alternative medicine and the perimenopause An evidence-based review

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The perimenopause is a challenging time of life for many women and for health workers caring for them. Many women assume that the degradation of ovarian function is a long, steady decline, characterized by a slow ebbing away of their estrogens. In reality, the perimenopause can be a stormy period of hormonal chaos, with unpredictable levels of estrogen, irregular ovulation, and diminishing peak levels of progesterone. Perimenopausal years, puberty in reverse, can be rapid or slow, tranquil or tempestuous, unnoticed or disorienting.

The members of the Council of Affiliated Menopause Societies have agreed that perimenopausal transition shall be defined as the period immediately before menopause when endocrinologic and biologic and clinical features of approaching menopause commence and the first year after menopause. The median onset is around 47.5 years of age. Perimenopause encompasses what is often termed *being in* or *going through* menopause. With the mean age of menopause being 51 years of age, perimenopause includes 3 to 5 years before and 1 year after the cessation of menstrual flow.

Perimenopause and menopause result from the progressive follicular depletion. The most rapidly progressive decline in fertility occurs after age 38 because of ovary senescence. Atresia of follicles accelerates at this age. Ovulation occurs less frequently, cycle length can increase or decrease, and in an effort to flag the failing ovary, follicle-stimulating hormone (FSH) rises in the early follicular phase. Although the peak number of follicles at 20 weeks' gestational age may be as high as 7 to 8 million and 1 million at birth, by age 40 residual follicle units generally has fallen to less than 25,000. These remaining follicle units exhibit functional impairments, less likely to achieve successful and complete maturation. Further down the course, the follicles become less responsive, increasing resistant to stimulation, and surviving units each produce less estradiol. In many cycles, in an effort to find a competent follicle, many follicles are recruited and occasionally

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estrogen levels are extremely high because of the overabundance of stimulated units, contrary to the popular impression that the perimenopause is a hypoestrogenemic state. Inadequate luteal phase develops with decreased progesterone peak and duration, and finally progesterone production ceases. Ultimately menopause arrives when the number of primordial follicles drops below 1000.

Menopause has classically been a retrospective diagnosis, determined at the point in time when a woman has been amenorrheic for 1 year. This clinical definition is of little use in dealing with the perimenopausal woman. Are we really interested in the last period? For patients and clinicians, milestones that are more important include (1) onset of symptoms; (2) loss of fertility, as defined by loss of truly viable follicles; and (3) estradiol loss and shift to estrone dominance.

In the perimenopause, characterized by erratic cycles and unpredictable estradiol levels, women begin to suffer the same sorts of symptoms associated with true menopause or castration. Treatment of the perimenopausal woman represents a greater challenge than the truly menopausal woman, because of the unpredictable, unstable ovarian function. Symptoms wax and wane, sometimes resolving spontaneously for months at a time, recurring without warning. Patients often keep detailed records of symptoms, in an effort to discern some pattern, to fabricate some order in a series of events that are random. Practitioners caring for women in the transitional years agree that treatment is more difficult than in the truly menopausal woman, given the quixotic appearance of symptoms and the presence of residual fertility, making concomitant contraceptive use an imperative.

Complementary and alternative medicine

Complementary and alternative medicine (CAM) includes an array of systematic practices that rely on physical assessments and physiologic constructs that differ from medicine as taught in Western health care institutions or on therapeutic modalities, which work beyond the confines of allopathic practice (Table 1). CAM is no longer confined to bicoastal elitist communities. In 1993, Eisenberg et al [1] estimated that at least 42% of Americans sought care from health practitioners other than traditional allopathic physicians and the percentage use today is even higher. Almost 50% of adult Americans are taking some sort of botanical or nutritional supplements or nutraceutical.

Although alternative medical practices often cannot provide statistical proof of efficacy, they offer subjective superiority, which patients find exceedingly appealing. Unhurried visits, comfortable settings, guarantees of success, overwhelming optimism, and individualization provide comfort in this day of increasingly impersonal managed care [2]. CAM seems also to provide so many options (nutrition, herbs, teas, foods, minerals, body therapy, meditations, and more), whereas conventional medicine seems to have only one limited offering for easing symptoms during the perimenopause and beyond: drugs.

Consumer demand, coupled with the support of the US Congress, has led to two defining events that have increased the acceptability and legitimacy of CAM

Table 1
Classification of complementary and alternative medical health practice

Alternative systems of medical practice
Acupuncture
Anthroposophically extended medicine
Ayurveda
Community-based health care practices
Environmental medicine
Homeopathic medicine
Latin American rural practices
Native American practices
Natural products
Naturopathic medicine
Past life therapy
Shamanism
Tibetan medicine
Traditional oriental medicine
Bioelectromagnetic applications
Blue light treatment and artificial lighting
Electroacupuncture
Electromagnetic fields
Electrostimulation and neuromagnetic stimulation devices
Magnetoresonance spectroscopy
Diet, nutrition, and lifestyle changes
Changes in lifestyle
Diet
Gerson therapy
Macrobiotics
Megavitamins
Nutritional supplements
Herbal medicine
Echinacea (purple coneflower)
Ginger rhizome
Ginkgo biloba extract
Ginseng root
Wild chrysanthemum flower
Witch hazel
Yellowdock
Manual healing
Acupressure
Alexander technique
Biofield therapeutics
Chiropractic medicine
Feldenkrais method
Massage therapy
Osteopathy
Reflexology
Rolfing
Therapeutic touch
Trager method
Zone therapy

(continued on next page)

Table 1 (*continued*)

Mind-body control
Art therapy
Biofeedback
Counseling
Dance therapy
Guided imagery
Humor therapy
Hypnotherapy
Meditation
Music therapy
Prayer therapy
Psychotherapy
Relaxation techniques
Support groups
Yoga
Pharmacologic and biologic treatments
Antioxidizing agents
Cell treatment
Chelation therapy
Metabolic therapy
Oxidizing agents (ozone and hydrogen peroxide)

(HYPERLINK http://altmed.od.nih.gov/oam/what-is-cam/classify.shtml http://altmed.od.nih.gov/oam/what-is-cam/classify.shtml.

in the United States. In 1992, the office of Alternative Medicine was started as a branch of the National Institutes of Health, with minimal funding of $2 million dollars, and even that small amount was thought by many to be a waste of tax money. The National Center for Complementary and Alternative Medicine, with a budget of $89 million, has become a major provider of funding for research on CAM practices. Moreover, the Congress passed the Dietary Supplement Health and Education Act, which exempts botanical medicines from drug regulatory processes by classifying them as dietary supplements. Supplements can be sold without oversight and testing by the Food and Drug Administration. Even though manufacturers are not allowed to make claims about prevention or treatment of disease, the advertisements for these products push the edge of the envelope. Maintaining mood becomes treatment of depression, and prostate health becomes treatment for benign prostatic hypertrophy. Appetite control morphs into the promise of weight loss without diet or exercise; wellness implies arresting the processes of aging; and a high-fiber laxative cleanses the body of toxins and poisons that may or may not exist. The general public, naively, believes that if a product is on store shelves it has been approved and tested for safety and efficacy. The reality is that supplements are exempt from such scrutiny. Adulteration and contamination are commonplace, and the data regarding clinical effects, side effects, and complications are little more than anecdotal, far short of scientific study.

The most recognizable and widely used CAM treatment is botanical medicine. Every pharmacy and grocery now routinely stocks a wide array of the vitamin

and mineral supplements, and often shelves full of botanicals. Large "organic" supermarkets devote yards of shelf space to "natural" products, like hair restoratives and homeopathic medicines.

Although the term *herbal* defines medicines made from the herbaceous portions of plants, namely the leaves and stems, *botanical* denotes foods and supplements made from any plant part (leaves, stems, seeds, fruits, flowers, and roots). Estimates are that 30% of the current pharmacopoeia is derived from old plant medicines, still grown in open fields, or a phytochemical that is now synthesized in the laboratory setting. Different plants are used to different therapeutic purposes, and different parts of the same plant may be used for different complaints. Plants are said to provide a number of actions that might be of importance to the reproductive systems including estrogenic, progestational, androgenic, and anti-estrogenic activity. In discussing the role of CAM in treating the perimenopausal woman, most of the information centers on botanical medicines as interventions.

Abnormal bleeding in the perimenopause

The endocrine basis for menopause suggests that a woman's periods simply space out over time and then finally stop. In fact, only 10% of women experience this kind of "normal" menopause. Other women suffer with a number of menstrual irregularities, skipping cycles, restarting, with increases and decreases in the amount of flow. The Seattle Midlife Women's Health Study defined three phase of change in menstrual flow, which occur during the perimenopause, regardless of the age of the transition: (1) early in the process the amount of flow and the cycle length change; (2) later there is cycle irregularity without skipping cycles; and (3) later still in the course, irregularity is further exacerbated with skipped cycles becoming more and more common. Cycles disturbances occur in 90% of women during the 4 to 8 years before true menopause.

Most commonly women seek care for menorrhagia or irregular cycles. Very few present complaining about oligomenorrhea or hypomenorrhea, unless they have hopes of a later life pregnancy. Women who have delayed childbearing who see spacing out of their cycles do recognize this signal as an ominous sign. The alternative treatment of fertility problems is beyond the scope of this discussion.

After proper evaluation and ruling out other causes, such as myomata uteri, abnormal pregnancy or missed abortion, thyroid dysfunction, and malignancy of the lower genital tract, the perimenopausal variants of dysfunctional uterine bleeding are treated by a number of conventional approaches that include the following:

1. Progestational therapy
2. Oral contraceptives
3. Gonadotropin agonists with add-back therapy
4. Nonsteroidal anti-inflammatory drugs
5. Progesterone- or progestin-releasing intrauterine devices
6. Endometrial ablation

Alternatives for menorrhagia

Many products are recommended. Some are supposed steroid antagonists, whereas others often are anticoagulants, and might alter cramps by easing the egress of menstrual flow. Recommended botanicals include the following [3]:

- Arnica (*Arnica montana*)
- Beth root (*Trillium erectum*)
- Burning bush (*Dictamnus albus*)
- Ergot (*Claviceps purpurea*)
- Great burnet (*Sanguisorba officinalis*)
- Horsetail (*Equisetum arvense*)
- Lavant cotton (*Gossypium herbaceum*)
- Maidenhair (*Andiantum capillus-veneris*)
- Nerve root (*Cypripedum calceolus*)
- Scotch broom (*Cytisus scoparius*)
- Shepherd's purse (*Capsella bursa-pastoris*)
- Sweet sumach (*Rhus aromatica*)

Although the German Commission E on botanical medicines has recommended shepherd's purse for menorrhagia, and although it is thought to contain an unknown hemostatic substance, there are no quality clinical studies of any of these herbals for this indication.

Hot flashes, vasomotor symptoms, and night sweats

Hot flashes are the second most common complaint associated with the perimenopausal age group. Eighty-five percent of women have vasomotor symptoms during the year preceding and following menopause. Some women continue to have hot flashes throughout their postmenopausal year. As many as 57% of women report having persistent, although not necessarily severe, hot flashes 10 years after their last menstrual period.

Estimates from scientific studies and consumer surveys suggest that 15% to 25% of women characterize their hot flashes and sweats as severe, degrading sleep, social activities, and other quality of life indicators. Physicians are likely to be approached by the most severe sufferers, whereas women with milder symptoms are less likely to ask for medication. Women with milder symptoms are very likely to look for over-the-counter products, seeking kinder, gentler therapeutic options for a process they perceive as a natural but nonetheless annoying problem.

Characterized by the sudden, transient sensation of heat spreading over the upper body, usually starting in the neck and face, then extending to the chest, back, and arms, the hot flash may also bring on flushing and sweating, and then a sensation of chilling. Other somatic symptoms may include palpitations, anxiety,

head stuffiness or fullness, nausea, and air hunger. In theory, loss of estrogen leads to a failure of thermoregulatory processes with the set-point for temperature regulation readjusted to kick in within the normothermic range, rather than in hyperthermic state. The subject first flushes and then cools even when core temperature is within normal range. At one time, it was thought that there were no discernable temperature fluxes with the hot flash, but now with sensitive monitoring, it is realized that the event is preceded by a 0.08°C temperature rise in 40% of women. The temperature rise is followed by a mild to moderate elevation of heart rate typically in the range of 4 to 35 beats per minute, and then followed by a profound peripheral vasodilation. Peripheral finger plethysmography demonstrates that flow rates can increase as much as 30-fold. Vasodilatation leads to facial flushing, and increases in skin temperature of 1°C to 7°C in fingers and toes. The sweating (sudorific) response then increases the radiation of heat to the environment, with a concomitant decline in skin temperature. Evaporative cooling from head and chest are most profound. Thirty percent of heat dissipation under normal environmental conditions occurs through the head and scalp. The profound sweating and evaporative cooling can lead to a significant drop in core temperature, below normal, provoking chills and shivering as the body then tries to rewarm back to a normal body temperature.

Hot flashes are very common in the perimenopausal age group, reported by 41% of women over age 39. Hot flashes occur in 85% of women in the years proceeding and following menopause. Some women continue to have hot flashes throughout their postmenopausal lives. As many as 57% of women report having persistent, although not necessarily severe, hot flashes for 10 years after the last menstrual period. Triggers include alcohol, spicy foods, exercise, hot or humid weather, and confined spaces.

Not all hot flashes are hormonally induced. Underlying infectious diseases, such as tuberculosis, and myeloproliferative diseases are associated with night sweats. Moreover, medications also may cause sweating. Most notable are the selective serotonin reuptake inhibitors (SSRIs), with head sweating being the most prominent feature. Other uncommon conditions to consider include carcinoid, pheochromocytoma, thyroid disease, and somatic stress-related disorders. Medications can also cause sweating.

Estrogen is the treatment of choice for vasomotor symptoms in the menopausal woman. A huge body of evidence has documented an 80% to 100% reduction in vasomotor complaints, depending on the underlying severity of symptoms and the dose of estrogen used. The mainstay of therapy for vasomotor symptoms in the perimenopause has come to be low-dose oral contraceptives. Casper reported a 50% reduction in number of hot flashes over that seen with placebo in such women taking a low-dose oral contraceptive [4].

Many drugs other than estrogen are suggested for management of vasomotor symptoms. Progestins, such as megestrol, norethindrone acetate, and medroxyprogesterone acetate, have documented success and also can be used to treat menorrhagia. More recently, the SSRIs in low doses demonstrated some efficacy in treating these complaints, with the added advantage of treating pre-existent or

underlying mood disorders that may have exacerbated during the perimenopausal transition. The effects of belladonna and phenobarbital combination products and clonidine are short lived. Moreover, the side effects of these pharmaceuticals are often unacceptable for the busy working woman.

Alternatives for vasomotor symptoms

Soy

The use of soy in perimenopausal women has not been specifically addressed. Study of soy has included only most menopausal women. The results are mixed. The outcomes are difficult to compare because of different amounts of soy protein in differing food stuffs with different amounts of the active component, the isoflavones. Moreover, studies have been of very short duration, less than 3 months. Representative studies include Washburn et al [5], where women were given 20 g of soy protein with 34 mg of isoflavones or a 20-g carbohydrate complex for 1.5 months. Hot flashes decreased in severity but not frequency in the treatment group. Albertazzi et al [6] studied more than 100 women with seven or more hot flashes per day, and randomized them to a 60-g soy protein supplement with 76 mg of isoflavones or to a casein control. Hot flashes decreased by 45% in the treatment arm, compared with only a 30% decrease in the control group. Murkies et al [7] gave women a soy flour supplement. After 3 months the soy group evidenced a 40% reduction, whereas the controls fed wheat flour experienced about a 25% decline. The difference was not significant.

Recently, Knight et al [8] conducted a randomized, double-blind, placebo-controlled, parallel-group trial with 24 postmenopausal women. After 3 months of treatment women on a dietary beverage with 60 g of soy protein with a total isoflavone concentration of 134.4 mg were compared with a control group ingesting the same shake but an isoflavone-poor version. There were no observed differences in the responses of subjects in hot flushes, Greene Menopause Symptom scores, vaginal maturation value, levels of FSH or sex hormone–binding globulin, or bone turnover markers. The soy group had a 25% drop-out rate from the study because of bad taste. Other studies have also had very high discontinuation rates in the soy arms because of gastrointestinal distress, gas, cramps, and stomach pains.

Black cohosh

Black cohosh (*Cimicifuga racemosa* L. Nutt, family, Ranunculaceae) goes by many folk names including black snakeroot and bugbane. Lydia Pinkham's Vegetable Compound was based on black cohosh plus 18% ethanol, and the amount of black cohosh is said to be similar to the amount in current commercial preparations. In Europe and the United States, an ethanolic extract is sold over the counter as Remifemin and is on the list of botanicals approved by the German Commission E for the treatment of the climacteric, premenstrual syndrome (PMS), and dysmenorrhea. Before the recognition of a potential link between estrogen and breast cancer, the basic science research of the manufacturer sought to prove that

black cohosh had estrogenic activity. The company, however, took a different tack after 1990, trying to characterize black cohosh as something other than estrogen.

Quality clinical trials are limited. Seven of eight published trials did not use placebo controls and seven of eight are only available in German. Duker et al [9] conducted a comparison of black cohosh with placebo using 40 mg twice daily (twice the standard dose) and found Remifemin suppressed hot flashes about 25% better than placebo in the 2-month trial. Another trial, not accessible in its full text form in English, compared this product, 40 mg twice daily, with conjugated equine estrogen, 0.625 mg, and with placebo. The herbal remedy provided good relief, whereas estrogen, surprisingly, performed no better than placebo. Closer scrutiny may explain this apparent contradiction to the basic understanding of the role of hormone replacement therapy. The study included premenopausal, perimenopausal, and postmenopausal women. Another study by Lehmann-Willenbrock and Riedel [10], which includes women presumed in many review articles to be menopausal, 60 subjects under the age of 40 posthysterectomy. This study is highly flawed as a proof of efficacy black cohosh in menopausal women. The women in this study were said to be post menopause. Careful reading however reveals that while all subjects had their uterus removed, one or both ovaries were retained in situ. Given that all women were under the age of 40, almost all would also retain a high potential for continued ovulatory ovarian function. Though they would not menstruate, they would not be truly menopausal if menopause is defined as ovarian failure, rather than simply the absence of menstrual periods. The study compared the efficacy of estriol 1 mg, conjugated equine estrogens 1.25 mg, estrogen plus progestin, and Remifemin 2 twice daily, but no placebo arm was included. All women had high menopausal symptom rating using Kupperman's index, and all treatment groups improved during the 6 month study period. This outcome proves only that given time and any sort of treatment modality, women who have multiple problems after surgical hysterectomy improve over time.

Studies in Germany by Schaper Brummer, the manufacturer of Remifemin, and by others reassuringly have demonstrated repeatedly that black cohosh has no estrogen activity in vivo. Recent studies looking at endometrial thickness, maturation index of the vaginal epithelium, serum leutinizing hormone, FSH, estradiol, and prolactin [11] confirm that black cohosh does not exhibit peripheral estrogenic effects. Black cohosh does not cause changes in renal, hepatic, or coagulation functions, and has no major side effects save for some minor gastrointestinal complaints.

The most recent publication on black cohosh was done in 85 breast cancer survivors. Subjects received placebo or black cohosh, 20 mg twice daily. Both treatment and placebo groups evidenced significant declines in number and intensity of hot flashes over time, but the differences between the groups were not statistically significant. This study may not be universally applicable. Fifty-nine of the 85 women were on tamoxifen. Only nine women who took black cohosh were not also taking tamoxifen, and these nine women had very marked reduction in symptoms, but the subset was too small for independent statistical analysis. These findings do not completely squash all hopes regarding black cohosh.

Tamoxifen may greatly dampen the effectiveness of black cohosh [12]. Further trials with meticulous study design are needed.

Dong quai

Dong Quai (*Angelica sinensis*) is also called dang gui and tang kuei (*Angelica polymorpha* Maxim. var Sinesis Oliv, aka A. sinensis [Oliv] Diels). The root is used as the female balancing agent in traditional Chinese medicine, and is a panacea for almost every gynecologic ailment including hot flashes, dysmenorrhea, oligomenorrhea, PMS, amenorrhea, and menopausal syndrome. It is also recommended as a laxative and antispasmodic, and as a treatment for insomnia, anemia, and hypertension. Dong quai is said to be "a warm herb that both circulates and nourishes blood, is also good for strengthening someone who is underweight, frail, anemic and chilly [13]." Dong quai is said to be estrogenic, because it has been associated with episodes of uterine bleeding and has uterotropic effects in ovariectomized rats.

There are no studies of dong quai specifically directed toward the perimenopause. Hirata et al [14] studied 71 women with FSH over 30 mIU/mL and randomized them to either 4.5 g dong quai per day or placebo. The outcomes, based on patient diaries and Kupperman index, found no differences in FSH, leutinizing hormone, estradiol, vaginal maturation index, and endometrial thickness. Critics suggested that the study design was inadequate because dong quai is never given alone, but rather always used in concert with other herbs, and that interaction of the botanicals provides a synergy needed for clinical effects. Nonetheless, in the real world dong quai is promoted and sold as a single botanical, often in very low doses, far lower than the 7 to 12 g used by some traditional Chinese medicine practitioners. One branded product of dong quai, Rejuvex, also contains bovine ovarian, uterine, mammary, and pituitary tissues. The ingestion of bovine brain and spinal cord tissue imposes a high risk for development of new variant Creutzfeldt-Jakob disease, also known as *bovine spongiform encephalopathy* or *mad cow disease*. Considering an absence of proved efficacy, adulteration with animal tissues, and potential for photosensitization, neoplasia, coagulopathy, and herb-drug interactions, practitioners should advise women to avoid dong quai.

Evening primrose

Evening primrose (evening star, *Oenothera biennis* L family onagraceae) is a source of linolenic acid, a type of omega-3 essential fatty acid. Other sources include cold water fish, canola oil, soybean oil, and a few vegetable oils. Gamma linolenic acid comes from seed oils of current, borage, and evening primrose. These fatty acids are eicosanoid precursors and are part of cell membranes. The pathway for dietary gamma linolenic acid leads to dihomo-gamma-linolenic acid, which in turn is converted by inflammatory cells to 15-(S)-hydroxy-8,11,13-eicosatrienoic acid and prostaglandin E_1, with potent anti-inflammatory activity. Gamma linolenic acid and dihomo-gamma-linolenic acid seem to affect inflammatory processes by regulating T lymphocytes, and gamma linolenic acid

inhibits angiogenesis. Evening primrose is recommended for a number of inflammatory and autoimmune processes. In reproductive medicine, evening primrose oil is used to treat mastalgia and mastodynia. The most publicized suggested uses have been for PMS and menopausal symptoms. There are seven studies of evening primrose oil for PMS, with five of the seven using blinding and randomization. The responses to evening primrose oil are no better than those resulting from treatment with placebo [15,16]. Similar null results were found in the one well-constructed clinical trial using evening primrose oil for menopause [17].

Ginseng

The genus name for many types of ginseng, *Panax*, derives from the word panacea, meaning cure-all. There has been one case of uterine bleeding occurring after a woman used a ginseng-containing face cream. Ginseng is widely promoted as a performance-enhancing supplement, promising stamina, speed, and endurance. For women, ginseng sings the most provocative of siren songs: the promise of weight loss without dieting or exercise. Different ginsengs are reputed to have different effects. Korean or Chinese ginseng claims to be most active as a stimulant, aphrodisiac, digestive, and anabolic agent and is promoted as a health tonic for the elderly. American ginseng is offered as the best "adaptogen." Siberian ginseng is supposed to be the best for athletic performance and endurance. Unfortunately, most of the literature on *eleutherococcus* is in Russian in studies done by the Soviet military and Olympic trainers, and not accessible in English.

Regarding menopause, Wiklund et al [18] recently reported a relatively large and long-term study of G115, the active ingredient in a commercial product sold in the United States and Europe called Ginsana. A randomized, multicenter, double-blind, parallel group study was done in 384 postmenopausal women over 16 weeks. Physiologic measures included FSH, estradiol levels, endometrial thickness, maturity index, and vaginal pH. In measuring overall symptom relief, the group receiving ginseng extract demonstrated a slightly better outcome than the controls but the trend did not reach statistical significance. When the subsets were sorted out P values less than .05 were identified only for depression, well-being, and health subscales, favoring ginseng compared with placebo. Ginseng had no effect on FSH and estradiol levels, endometrial thickness, maturity index, and vaginal pH, and hot flashes were no better in the treatment versus placebo arms [18].

Soy- and red clover–based isoflavone supplements

Soy and red clover, *Trifolium pratense*, are legumes and rich sources of a large number of phytoestrogens. Although soy is the most common source of isoflavones in the human diet, red clover is the richest source of isoflavones of any plant. Red clover is also a rich source of coumestans, a phytochemical with steroid like activity.

A number of isoflavone isolates are being promoted in the United States as alternatives to isoflavones from soy foods. The source plant material is washed with alcohol and the isoflavones, which are alcohol soluble, are extracted. The alcohol is evaporated off and the remaining isoflavone residue is packaged as a food supplement. Literature promoting the use of isoflavone isolates refers to observational studies on populations who consume high soy diets, and then suggest that supplements can provide similar health benefits. Products like Healthy Woman from soy and Promensil from red clover are being heavily promoted as alternatives to pharmaceutical estrogens here and abroad.

Trials of various isoflavones isolates for hot flashes have been equivocal. A red clover–derived commercial preparation containing 40 mg total isoflavones was given to 51 women, whereas 43 women received a placebo. Barber et al [19] found after the 6-month crossover trial that the product was not more effective than placebo. Hot flash frequency decreased in both groups, 18% and 20% in treatment and placebo, respectively. No differences were seen in other symptoms (Greene Scale) or endometrial thickness (ultrasound). Knight et al [20] studied the same product using isoflavone, 40 mg, 160 mg, or placebo for 12 weeks. Hot flash frequency decreased in all groups by 35%, 29%, and 34%, respectively. There were no differences from baseline in FSH or sex hormone–binding globulin. Isoflavone isolates cost around $22 to 50 per month. The evidence does not support this kind of extravagant expenditure.

Topical progesterone

Progesterone creams are sold over the counter in health food stores as menopausal and perimenopausal supplements. Progesterone is absorbed through the skin and then is said to affect an amazing array of biologic functions. Claims about progesterone cream are widely publicized and first appeared in a book by Lee [21]. Most of the references in the bibliography of the book are actually studies done with medroxyprogesterone acetate or one of the C-19 nor testosterone derivatives. Lee [22] claims to have a series of 100 patients using progesterone cream as a treatment for osteoporosis. During the 3-year study period, he cites an average increase in bone mineral density in the lumbar spine of 14% in the 63 women (not 100) who actually had sequential bone mineral density measures during the course of their care. Harkening back to Lee's first publication of his "series," one finds that two thirds of the women in his study population were also taking conjugated equine estrogens. The greatest improvements were seen in women with the worst bone density. Lee did not include any control group in his population. He states, "It does not require double-blind placebo controlled experiment to conclude that progesterone, used in this fashion, is of great benefit in treating (and preventing) osteoporosis." Most papers cited by Dr. Lee refer to studies done using progestational agents other than natural micronized progesterone. The progestin used in studies include medroxyprogesterone acetate and the nortestosterones, like norethrindrone acetate, the progestins commonly used in oral contraceptives.

Leonetti et al [23] tried to reduplicate Lee's [22] results. They randomly assigned 102 healthy women within 5 years of menopause to transdermal progesterone cream or placebo. Women used a quarter teaspoon of cream (containing 20 mg progesterone or placebo) to the skin daily plus multivitamins and calcium, 1200 mg. Bone scans and serum chemistries were repeated after 1 year. Thirty (69%) of 43 in the treatment group and 26 (55%) of 47 in the placebo group complained initially of vasomotor symptoms. Improvement or resolution was noted from diaries in 25 (83%) of 30 treatment subjects and 5 (19%) of 26 placebo subjects ($P < .001$). No differences were found in bone mineral densities between the groups. The authors concluded that although topical progesterone used in this manner improved symptoms, it offered no substantive bone benefits.

Recently, progesterone creams have been promoted by word of mouth and in consumer seminars as substitutes for oral progestational therapy in women taking exogenous estrogens. Anasti et al [24] reported adequate suppression of proliferation using transdermal progesterone for 1 month with oral estrogen. A longer study is in progress. Serum levels of progesterone by the transdermal route are highly variable, and no studies can document the adequacy of this approach in limiting the risk of endometrial hyperplasia over the long term Women who choose to use progesterone cream as the progestational arm of their hormone replacement regimen should be evaluated with annual endometrial biopsy, just as though they were taking unopposed estrogen.

Cognition, mood, affect, depression, anxiety, and sleep

Mood disorders associated with the perimenopause clearly overlap with PMS and premenstrual dysphoric disorder (PMDD). Menopause as an event does not cause depression in otherwise stable women. Administration of exogenous estrogen to psychologically well women does not improve their moods or cognition. It needs to be stated, however, that 20% of women have experienced major mood disorder during their lives, and an additional 20% to 30% have had less severe depressive episodes. The pool of women at risk for exacerbation or recurrence of symptoms ranges from 30% to 40%, although women with classically defined PMDD constitute only 3% to 5% of the adult female population.

Ovarian steroids directly or indirectly influence neurotransmitters. PMS and other PMS-like symptoms seem to be the result of abnormal behavioral responses mediated by the central nervous system and triggered by the normal endocrine events. Presently, the mediator in PMS and PMDD is unidentified. The abnormal hyperreactivity of some women to changes in normal endogenous levels of sex steroids may be tied to the serotonergic system. The symptom complex associated with PMS and PMDD and the perimenopause (depressed mood, irritability, dietary cravings, and hostility) parallel many of the features of depression, and PMS has been treated successfully with SSRIs. Adrenergic, opioid, and γ-aminobutyric acid (GABA) systems have also been suggested to play roles in hormonally sensitive

subjects. The opioid system is said to be highly affected by the withdrawal of estrogen in the late luteal phase. Studies have shown correlation between brain neurotransmitters, neuropeptides, and sex steroid hormones, such that the synthesis and release of norepinephrine, dopamine, serotonin, gonadotropin-releasing hormone, beta-endorphin, corticotropin-releasing factor, and prolactin all are potentially modified by estrogens and progestins [25].

The SSRIs have become the linchpin of treatment of hormone-related mood disorders, and are safer and more effective than the older tricyclics antidepressants. Other agents that may have some use include buproprion (Wellbutrin), nefazodone (Serzone), and citrapolam (Celexa). Most gynecologists would do well to avoid the tricyclic antidepressants and monoamine oxidase (MAO) inhibitors. If a patient does not respond to an SSRI or similar drugs, referral should be made for more advanced psychiatric consultation.

Alternatives for mood and affective complaints

The quality of research on alternatives for mood disorders suffers greatly because of poor methodology and often fails to diagnose women accurately before entering trials. Many women included in trials have been self diagnosed, or diagnosed by a generalist. The studies do not confirm or screen any further for *Diagnostic and Statistical Manual IV*–defined characteristics. Moreover, many herbal manufacturers use their own proprietary psychologic screening and assessment tools, rather than using standardized tests. The results often are difficult to duplicate and compare. Women with atypical depression or dysthymic disorder may be lumped incorrectly with PMS or PMDD cases.

Most studies of alternatives for mood and affect have been done in menopausal women or in women with PMS. One can extrapolate safely from these two populations to the perimenopause, because complaints are very similar.

Ginkgo

Ginkgo biloba, also know as *maidenhair tree*, *Asiatic ginseng*, *Chinese ginseng*, and *Wonder-of-World*, is a very old tree whose leaf extract contains a variety of active flavonoids and terpenes. The plant has been used for medicinal purposes in traditional Chinese medicine for hundreds of years. Yet another panacea, it is recommended to slow aging; enhance cerebral blood flow; and in the treatment of multi-infarct dementia, Alzheimer's disease, and memory loss. It is also used to treat circulatory disorders, tinnitus, PMS, impotence, stroke, shock, headaches, hyperlipemia, hepatitis, asthma, colitis, and cochlear deafness. Ginkgo has demonstrated ability to increase blood flow and tissue perfusion, and stimulates the production of prostaglandins. It also has some catecholamine activity.

Clinical trials have found that improvements in cognitive symptoms of Alzheimer's disease and multi-infarct dementia may possibly be from increased blood flow, decreased red blood cell aggregation, and blood viscosity. The effects in Alzheimer's disease may also be caused by increasing the level of neurotransmitter, including muscarinic, alpha-2 acetylcholine, norepinephrine, sero-

tonin, and GABA. There are even a few well-designed trials suggesting some improvements in cognitive function in patients with dementias. Clinical studies on cognition and memory in otherwise healthy individuals have been less encouraging. There are no specific studies in midlife women addressing the mood or cognitive changes associated with hormonal loss. The most that can be said is that ginkgo has been found to be an effective adjuvant therapy in treating antidepressant-induced sexual dysfunction [26].The dose advocated for this indication is 60 to 240 mg/d. Because ginkgo causes decreased platelet and red cell aggregation, care should be exercised in recommending it to patients on anticoagulants, aspirin, and nonsteroidal anti-inflammatory drugs. Spontaneous subdural, subarachnoid, retinal, and other bleedings have been reported.

Kava (Piper methysticum)

The kava shrub and the roots grown in the south Pacific contain pharmacologically active compounds known as *kavapyrones* [2]. Kava drinks are used in many ritual settings in the Pacific islands for spiritual and amusement purposes. The most commonly studied product is an extract called WS 1490, which contains 70% kavapyrones. Kava acts very much like the benzodiazepines. Suggested sites of action include the limbic center and GABA receptors. Kava, however, does not bind directly to benzodiazepine receptors. Kava also inhibits norepinephrine uptake, antagonizes dopamine, inhibits MAO-B, and decreases glutamate release, but does not interact with opioid receptors. Seven randomized trials have been done, most often comparing kava with benzodiazepines. Overall impressions are that kava provides significant reductions in anxiety scores, but the sample sizes are small, and the criteria for admission to the trials have been quite variable. Although not studied specifically in perimenopause or menopause, kava offers some interesting possibilities in treating anxiety and insomnia. Side effects include disorientation and intoxication. Alcohol and the use of other sedative hypnotics may potentiate kava's effects. More recently, cases of hepatic failure have been reported with the use of kava from Europe. Medwatch recently sent a "Dear Doctor" letter soliciting any suspected cases of hepatotoxicity related to kava use. It stated that "Approximately 25 reports of hepatic toxicity associated with the use of products containing kava extracts have been reported …. Serious hepatic adverse effects include hepatitis, cirrhosis, and liver failure. At least one patient required a liver transplant." Several European countries have now banned kava sales pending study of cause of the liver damage in these cases [27].

St. John's wort (Hypericum perforatum)

Extracts of this flower have been used for centuries to treat mild to moderate depression. The constituents include hypericin, pseudohypericin, and flavonoids. Several mechanisms of action for the psychotropic effects of St. John's wort have been proposed but not confirmed, including (1) inhibition of MAO and catechol methyltransferase, (2) decreased corticotropin-releasing hormone and then lowering levels of cortisol or affecting GABA receptors in the brain, and (3) serotonin receptor blockade. St. John's wort inhibits norepinephrine, serotonin,

and dopamine reuptake. Hypericin, once thought to be the primary active ingredient, serves as a standardization marker for commercial alcohol extract products. Hypericin does not seem to be an MAO inhibitor. Although products are often standardized to contain 0.3% hypericin, many preparations are now standardized to the hyperforin content, thought to be the active ingredient. St. John's wort extracts have gained popularity as an alternative self-care medication for treating dysphoria, mild depression, and other mood disorders.

Most studies of St. John's wort have compared the herb with tricyclic antidepressants, often in subtherapeutic doses. Trials comparing St. John's wort with SSRIs are limited by small size, no placebo arm, short duration, and differing preparations. Fifteen controlled trials have been reported and assessed by meta-analysis by Linde [28]. Combined analysis of 1757 cases found that hypericin in doses less than 1.2 mg/d led to a 61% improvement in mild to moderate depression, whereas higher doses up to 2.7 mg/d produced a 75% improvement. Some have suggested that St. John's wort is helpful in treating seasonal affective disorder. The herb seems to be ineffective for severe depression. Reports that *H. perforatum* compares favorably with antidepressant drugs, such as amitriptyline, imipramine, and more recently fluoxetine, are overblown. In most studies, the doses of antidepressant used were suboptimal [29]. In July 1999, the US National Institutes of Mental Health began a 3-year study testing St. John's Wort. The 336 patients have been enrolled at 12 centers, and will receive 900 mg of extract of St. John's wort (identical to a branded product made by Kira), sertraline, or placebo. A small trial with 30 patients found that St. John's wort performed as well as sertraline, 75 mg [30].

Side effects are similar to but far less than with standard antidepressant medications, including dry mouth, dizziness, and constipation. Other problems include gastrointestinal upset, sedation, fatigue, and confusion. St John's wort is also potentially photosensitizing, and recent concern has been raised about an increased rate of cataracts in users. A body of literature is emerging documenting profound drug-herb interactions with St. John's wort. St. John's wort lowered levels of the protease inhibitor indinivar so profoundly as to render the drug ineffective [31]. St John's wort drug-herb interactions [32] include potential interactions with serotonin-reuptake inhibitors; decreased bioavailability of digoxin, theophylline, cyclosporin, and phenprocoumon; and lower levels of oral contraceptives, calcium antagonists, metoprolol, propranolol, phenytoin, rifampin, midazolam, and other anesthetics, acting as potent stimulus of the cytochrome P450, particularly the CYP3A. St. John's wort induces changes in the drug efflux transport P-glycoprotein and subsequently may affect levels of drugs that are substrate for this system [33]. Anesthesiologists are advising the discontinuation of all botanicals at least 2 weeks before elective surgery. St. John's wort has not been effective in the treatment of major depression.

Valerian

The common valerian or garden heliotrope (*Valeriana officinalis* L valerianaceae) has been used for ages as a tranquilizer and soporific. The effective

constituent has never been identified, but is thought to be a GABA derivative. A similar GABA-like compound has been found in chamomile, which also is proffered as an herbal sleep aid. Before the advent of benzodiazepines and barbiturates, many psychiatric disorders were treated with valerian. Although having no demonstrable toxicity and degrading rapidly, there have been some reports of dystonic reactions and visual disturbances, perhaps mediated by other drugs used concomitantly or because of the preparation When taken as an extract, tea, or alcohol tincture it seems to provide some mild, limited sedating and calming effects without the lingering metabolites that continue to circulate after taking diazepam. After L-tryptophan was taken off the market, valerian enjoyed a resurgence of popularity. Studies on sleep architecture have found that valerian is best at reducing sleep latency, prolonging stage 2 non-rapid eye movement sleep, and decreasing rapid eye movement and slow-wave sleep duration [34]. EEG studies have failed, however, to confirm these effects.

Little is known about its actions, effects, or potential drug-drug interactions. Note that despite its lack of toxicity, botanical texts advise against use during pregnancy and lactation. Although adverse events are rarely reported, a recent case report attributed high-output congestive heart failure, tachycardia, and delirium to acute withdrawal prolonged use of large amounts of valerian [35]. It is best to avoid taking valerian when drinking alcohol or taking sedative-hypnotic drugs, since excessive or prolonged sedation may occur.

Summary

Alternative medicine is no longer mystical, mythical, or remote. At last 50% of the adult population has tried some sort of alternative therapy. As the population ages, and chronic illness becomes more prevalent, the use of alternatives is likely to continue to increase. CAM often targets chronic disorders that are often poorly addressed by conventional care, such as headache, arthritis, insomnia, fatigue, and so forth. Managed care, indirectly by imposing barriers to access and directly by offering riders that cover CAM services, are pushing patients away from more expensive conventional therapies.

In conditions like the perimenopause, where the symptoms may wax and wane unpredictably, quality research is needed to demonstrate the efficacy of interventions. In the not so distant past, CAM practices have been given a pass, permitted to lay claim to historical uses as proof of efficacy. This exemption from the rules has been revoked. Major journals have issued a call for a new, more evenhanded approach. The editors of the prestigious *New England Journal of Medicine* asserted that [36]:

> There cannot be two kinds of medicine – conventional and alternative. There is only medicine that has been adequately tested and medicine that has not, medicine that works and medicine that may or may not work. Once a treatment has been tested rigorously, it no longer matters whether it was considered alternative at the outset.

The *Journal of the American Medical Association* also reinforces the call [37]:

> There is no alternative medicine. There is only scientifically proven, evidence-based medicine supported by solid data or unproven medicine, for which scientific evidence is lacking. Whether a therapeutic practice is 'Eastern' or 'Western', is unconventional or mainstream, or involves mind-body techniques or molecular genetics is largely irrelevant expect for historical purposes and cultural interest.

Gynecologists and others who care for women need to be aware of the evidence supporting or refuting the claims made for both conventional and alternative medicine. Any therapy that provides effective and safe mitigation of the tumultuous and distressing endocrine events associated with the perimenopausal transition should be offered and used. An expanded array of therapeutic options may increase the likelihood of successful treatment and promote enhanced satisfaction and well-being for women. Such improvements can help to cement long-term relationships between providers and patients, for health and well-being now and in the future.

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Contraceptive needs of the perimenopausal woman

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Although there are many definitions of the perimenopause, all include the concept of transition from physiologic ovulatory menstrual cycles to hyperestrogenic anovulation and ultimately to hypoestrogenic ovarian shutdown. With this comes a transition from childbearing, and its requirement for contraception, to the infertility of menopause. Fecundity, the average monthly probability of conception, begins to decrease at age 40 and declines by 50% at age 43 [1]. This relative infertility is believed to be caused primarily by oocyte quality; but age-related uterine factors along with ovarian and neuroendocrine mechanisms have been proposed [2]. Also factored into the equation is the declining fertility of the male partner after the age of 50 [3]. Studies, however, support the fact that 80% of women between ages 40 and 44 at risk for pregnancy are still able to conceive [4]. For these women, contraception remains an important health issue.

With the prevalence of tubal sterilization in the United States, the need for contraception for the perimenopausal is often overlooked. Physicians, in an error of omission, may not discuss desire for childbearing or contraceptive practices. Regardless of their previous desire for pregnancy, perimenopausal women frequently have reached a point in their lives where an unplanned pregnancy is most often an unwanted pregnancy. This may be the basis for the reported abortion rate of 35% in women over the age of 40, and an even greater rate in women over age 45, the highest rate for any age group except for preteens [5]. These numbers are difficult to estimate in that the rates reported by the Alan Guttmacher Institute are consistently higher than the rates reported by the Centers for Disease Control and Prevention (CDC). This may be especially true for the rate in women over age 40 because these women are more likely to keep the abortion procedure confidential and may be less likely to confide even in their primary health care provider.

Risks of pregnancy and childbirth

The consequences of an unintended pregnancy in a perimenopausal woman go well beyond the abortion issue and must include the increase in pregnancy

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mortality and morbidity related to age. Although age alone may not be a risk factor, age-related medical problems are well-documented.

The CDC defines a pregnancy-related death as one that occurs during pregnancy, or within 1 year after a pregnancy, and is caused by pregnancy-related complications. Every day in the United States, two to three women die because of a pregnancy-related complication [6]. Although the risk of pregnancy-related death has decreased over the last 50 years, there has been no decrease in risk since 1982. The most recent data, 1996, indicate that the maternal mortality rate in the United States has remained at approximately 7.5 maternal deaths per 100,000 live births [7]. The risk of death because of pregnancy varies greatly by race and ethnicity [8]. Currently, the leading causes of maternal mortality are hemorrhage, pulmonary embolism, hypertensive disorders of pregnancy, sepsis, anesthesia complications, and cardiomyopathy. Other risk factors include lack of prenatal care, smoking, being a teenager, and less formal education [6].

It is estimated that 30% of all pregnancies have a pregnancy-related complication before, during, or after delivery. The most common causes of maternal morbidity are spontaneous abortion, ectopic pregnancy, hyperemesis, diabetes, hemorrhage, and infection. Childbirth is the most common reason for hospitalization in the United States and complications of pregnancy contribute to this rate. Childbirth-related complications account for more than 2 million hospital days a year with a cost of greater than $1 billion [6].

Contraceptive choices

There is no contraceptive method that is contraindicated merely by age. The contraceptive needs of the perimenopausal woman, however, may be better suited to some methods over others. These needs may be influenced by a desire for permanent sterilization; frequency of intercourse; need for protection from a sexually transmitted disease; or a desire for noncontraceptive benefits, such as control of the menstrual cycle, hot flushes, and prevention of gynecologic cancers and osteoporosis. These factors change throughout a woman's lifetime and what may be her choice at age 20 may not be the same choice at age 45.

Female sterilization

Female sterilization is the most common method of contraception used by perimenopausal women in the United States This may be because it is the only contraceptive method covered by most health insurance policies, but more likely because of unwarranted fears of other highly effective contraceptive methods (oral contraceptives [OCs], intrauterine devices [IUDs], and so forth). At one time it was believed to be the most effective form of contraception. Based on evidence from the CDC's Collaborative Review of Sterilization Working Group, however, it is as effective, not more effective, than many other very effective methods. The

failure rate is method dependent and ranges from 0.75% to 3.65% [9]. It requires an outpatient surgical procedure and costs are in the range of $3500 [10]. The side effects are short-term postoperative pain and a small surgical scar. The risks are directly related to a surgical or anesthetic complication, which is more closely related to body habitus and general health than to age. This method provides no inherent protection from sexually transmitted diseases. Although there is a common belief that sterilization leads to less normal menstrual cycles, the best evidence is that there is no relation to menstrual cycle control, either negatively or positively [11]. There is evidence that there may be a reduced risk for ovarian cancer secondary to sealing off the peritoneal cavity from the possibility of transmitting carcinogens through the tubes [12]. Sterilization regret, common in younger women, is much less common in perimenopausal women [13].

Barrier methods

Barrier methods are appropriate for any age group and may be very appealing to a perimenopausal woman with infrequent exposure. These methods average 85% efficacy and would probably be higher if studied in this specific age group with expected higher compliance than in younger age groups. If the woman assumes she probably cannot get pregnant anyway, however, compliance may go in the other direction. An advantage is that these methods are totally patient-controlled and do not require any additional care from the health care provider (other than an initial diaphragm fitting). The side effects are rare (latex allergy, bladder irritation, and decreased sensitivity of male partner) and there are no reported health risks. There are no noncontraceptive benefits, however, and they do not contribute to menstrual cycle control.

Periodic abstinence

The typical menstrual pattern of the perimenopausal woman is unpredictable. Cycles are usually shorter by 2 to 7 days, although longer cycles are almost as common. Irregular bleeding becomes normal. The quality of bleeding also changes, usually heavier at first followed by lighter bleeding as menopause approaches. Spotting before menses, secondary to an inadequate level to support the endometrium through the full cycle, is also common [14]. These menstrual patterns make ovulation prediction or the rhythm method very difficult for the perimenopausal woman without the addition of basal body temperatures or examination of cervical mucus.

IUDs

Intrauterine devices may offer the perimenopausal interesting options for contraception. Both the copper-containing IUD and the levonorgestrel intrauterine

system offer highly efficacious and long-acting methods [15]. The copper-containing IUD is effective for up to 10 years and the levonorgestrel intrauterine system for 5 years. Either method should get these women through their perimenopausal years. Each requires insertion by a health care provider, but little in the way of maintenance thereafter. The copper-containing IUD may have the disadvantage of increased menstrual bleeding and dysmenorrhea in some women, adding to the already abnormal uterine bleeding of the perimenopause. This may be reversed by nonsteroidal anti-inflammatory agents. The intrauterine system may add the specific benefit of therapeutic levels of a progestin to the endometrial cavity, avoiding the hyperplastic effects of unopposed estrogen during a perimenopausal anovulatory cycle and, potentially, decreasing dysmenorrhea [16]. The well-established risks of IUD use are infection within 20 days of insertion, perforation at the time of insertion, and ectopic pregnancy should there be a contraceptive failure. The intrauterine system also increases the risk of amenorrhea, although many women consider this a benefit, not a risk [16]. These risks, however, should be no different for the perimenopausal woman.

Injectables

The injection of medroxyprogesterone acetate has been available in the United States for a number of years. It is highly efficacious and is administered every 3 months by deep intramuscular injection. The common side effects are weight gain, bloating, headache, acne, depression, and a delayed return to fertility, the latter being a contraindication for perimenopausal women desiring a future pregnancy. Of greater concern to the perimenopausal woman is the irregular and random bleeding before reaching the goal of complete amenorrhea. Also of concern in this age group is the evidence that users of medroxyprogesterone acetate run the risk of bone loss and osteoporosis compared with controls [17,18]. Recently approved in the United States is a monthly injection of medroxyprogesterone acetate combined with estrogen, which has been shown to result in scheduled regular withdrawal bleeding, a rapid return to fertility, and a high level of patient satisfaction [19]. Although not studied specifically in perimenopausal women, the addition of estrogen may make this method attractive to this age group because of better cycle control and prevention of osteoporosis. Other noncontraceptive benefits have not yet been studied. This method's requirement of a monthly visit to a health care provider may be a deterrent to increasing its popularity.

Implants

The subcutaneous hormonal contraceptive implant system has never been highly popular in the United States. With its common side effects of random bleeding, headache, and depression, it is unlikely that it appeals to the perimenopausal woman.

OCs

The history of the use of OCs in perimenopausal women has been interesting. With the publication of the 1970 findings of the Royal College of General Practitioners stating that the original high-dose OCs may increase the risk of serious cardiovascular diseases [20], OCs were contraindicated in any woman over the age of 35. This held true until 1991 when the Food and Drug Administration re-evaluated the evidence and realized that the risk was confined to smokers and that the age of the nonsmoking user was not related to cardiovascular risk. This evidence was summarized by the World Health Organization and reaffirmed in a recent study by Rosenberg et al [21–23].

The OCs offer a very effective method of contraception, with efficacy rates of over 99% with perfect use [24]; however, only 11% of women age 40 to 44 and 4% of women age 45 to 50 are using OCs [25]. This is likely caused by the perception of serious health risks of OCs common in women of this age group [26–28]. Over the past 30 years, the doses of estrogen and progestogen contained in OCs have been drastically reduced, with a corresponding reduction in many of the health risks previously reported with the older formulations (generally containing 50 μg or more of estrogen). In fact, the last several decades have seen an abundance of studies demonstrating the absence of excess risk of myocardial infarction or stroke, regardless of age of the OC users or dose of the OC, when controlled for smoking and hypertension [22,26,29–32]. Even venous thrombotic events, the one remaining excess cardiovascular risk of today's estrogen-containing OCs, is not related to age of the OC user and does not increase the risk beyond that of age alone [33].

Simultaneously, there is an abundance of studies demonstrating important noncontraceptive health benefits conferred by OCs beyond the direct benefit of prevention of unintended pregnancy. Relative to the widespread dissemination of information about OC-associated health risks, however, these benefits have not been discussed very intensively in the media and by the lay population [34,35]. Concern about the safety of OCs, especially by perimenopausal women, is a common reason for noncompliance and early discontinuation [36,37]. Conversely, women who are aware of the noncontraceptive health benefits of OCs are more likely to be satisfied with this method of contraception [38]. These are not unexpected findings given that numerous misconceptions still abound about the safety of OCs and limited awareness of some of their most beneficial, and even lifesaving, effects [35,37].

The best established and consistently demonstrated major benefit of OCs is reduction in risk of ovarian cancer [39]. Cohort and case-control studies have shown that OCs lower the risk of malignant and borderline epithelial ovarian cancer in a duration-dependent manner. In a large US population-based case-control study conducted by the National Institute of Child Health and Development and the CDC (Cancer and Steroid Hormone Study [CASH]), a group of women with epithelial ovarian cancer was compared with an age-matched control group of women without ovarian cancer to evaluate potential associations between

risk of ovarian cancer and OC use [40]. The risk in women who had ever used OCs was 40% less than that of never-users. This risk was further reduced in women who reported longer use and in those who had begun using OCs for 5 or more years before the study. The greatest reduction in risk of disease (80%) was seen in women using OCs for 10 or more years. Reduction in risk was not related to specific OC formulations.

The results of this large study confirmed numerous earlier reports that the overall risk of ovarian cancer in OC users was significantly lower than in nonusers, regardless of the length of use. This is particularly important for perimenopausal women who ask, "Is it ever too late to start?" In a review of 14 studies conducted between 1977 and 1988 (including the CASH study described previously), Schlesselman [41] reported a consistent reduction in ovarian cancer risk with OC use. For studies that examined risk reduction relative to duration of OC use, the results consistently showed that risk reduction of approximately 40% occurs with 3 years of use, with further decline seen with longer duration of use. This is important information to help perimenopausal women understand that the longer the time on OCs, the greater is this benefit. Two meta-analyses of data from published studies were performed to assess quantitatively the risk of ovarian cancer with ever-use of OCs [42,43]. Both confirmed the highly statistically significant protective effect. Two subsequent analyses confirmed this association [44,45], including one that showed a reduced risk of ovarian cancer in women with a familial history of ovarian cancer, who have a higher risk of this disease [46]. Overall, the risk reduction seen in these studies is durable, persists between 10 and 19 years after cessation [40,42,45], and does not seem to be associated with any specific estrogen-progestogen dose or formulation [40,45].

Although the protective effect of OCs against ovarian cancer is well established, it has not been clear if this protection applies to the 10% of cases of invasive epithelial ovarian cancer that are hereditary. In a case-control study, the lifetime history of OC use was obtained from 207 women with hereditary ovarian cancer and a pathogenic mutation in either *BRCA1* or *BRCA2* and their sisters. A 60% reduction in risk was associated with the use of OCs for 6 or more years for carriers of either gene mutation [46].

The reputed mechanism that protects against ovarian cancer is suppression of ovulation. This theory is supported by evidence suggesting that incessant ovulation contributes to neoplastic growth [47], and by the finding that different OC formulations suppress ovulation to the same extent and also offer similar levels of protection against this cancer risk [40]. There are little data available, however, for newer OCs containing Ethinyl Estradiol (EE) 20 μg and their ability to suppress ovarian cancer is currently unknown. As with ovarian cancer, OC use lowers the risk of endometrial cancer in a duration-dependent manner. The CASH study also examined the relationship between OCs and cancer of the endometrium [48,49]. The overall risk of endometrial cancer in women who had ever used OCs was half that of never-users [48]. The protection was independent of the specific formulation, progestogen dose, or estrogen dose. In two subsequent reviews of epidemiologic studies that examined the effects of OCs on the incidence of uterine

neoplasia (including the CASH study) [48], the substantial duration-related protective effect of OCs on uterine cancer was consistent across the studies [43,50]. The protection persisted for at least 15 years after discontinuing OC use, and was independent of estrogen and progestogen doses and the formulations used. These results were later confirmed in a case-control study [51].

The suggested protective mechanism is that the progestogen in OCs counteracts or reverses the endometrial proliferative effect of unopposed estrogens and reduces estrogen-associated endometrial hyperplasia [48]. Considering the frequency of anovulatory cycles in perimenopausal women and their subsequent risk for endometrial hyperplasia, this benefit is of greater value than to the younger OC user.

Another malignancy that becomes more common during the perimenopausal years is colorectal cancer. Studies of the impact of OCs on colorectal cancer are more equivocal than with ovarian or endometrial cancers. A recent analysis of two case-control studies suggests that OC use lowers the risk of colon and rectal cancer [52]. Longer duration of use was associated with greater protection against colon cancer, but not with greater protection against rectal cancer. Other studies have found either a similar protective effect [53,54] or no effect of OCs on colorectal cancer [55]. A recent meta-analysis, however, found a greater than 50% reduction in this cancer in women who were current users and an 18% reduction in ever-users of OC [56]. The protective mechanism may arise from the estrogenic component of OCs, because estrogen-replacement therapy seems to provide duration-of-use-related protection against colon cancer and its mortality [57,58]. This estrogen effect may be mediated through hormonally induced changes in the composition of bile [59] or through a direct effect on gastrointestinal mucosa cell growth [60].

Another well-established noncontraceptive benefit of OC use is a reduction in the incidence of pelvic inflammatory disease. Typical results come from a recent large multicenter case-control study [61]. The risk of pelvic inflammatory disease was reduced by half in recent OC users compared with nonusers during this period. The protective effect was primarily evident in current users who had 12 months or more of OC use. Protection was seen after adjustments were made for medical history, sexual history and activity, and availability and use of health care. Potential mechanisms for reduction in pelvic inflammatory disease include thickening of cervical mucus causing a mechanical or chemical barrier to infectious organisms, reduced menstrual flow providing less favorable conditions for bacterial growth, and decreased retrograde menstruation [61]. Because this noncontraceptive benefit is not related to age or duration of use, however, it should have no unusual appeal to the perimenopausal woman.

More relevant noncontraceptive benefits of OCs are reduced effects in functional ovarian cysts, uterine fibroids, and endometriosis. The beneficial effects of OCs on reducing the number of retention or functional ovarian cysts was first demonstrated 28 years ago with OC formulations containing high-dose estrogen (≤ 80 μg) [62]. It was readily apparent that this beneficial medical effect translated into significant reductions in hospitalizations for surgery to treat

functional ovarian cysts. An approximate 50% reduction in functional cysts was demonstrated in women receiving OCs in the United Kingdom. The risk reduction for corpus luteum cysts was even greater at 78% [63].

Since these early reports, however, there has been some debate as to whether the newer low-dose monophasic and multiphasic OC regimens provide a similar benefit to that reported with older high-dose regimens, or even that they produce an adverse effect on cysts, as has been suggested by anecdotal reports [64]. Protection against developing ovarian cysts may be attenuated with low-dose monophasic pills and multiphasic regimens when compared with the high-dose (50 to 100 μg EE) monophasic regimens that were used in the past [65,66]. It is important to confirm these benefits in low-dose OC users (< 50 μg EE) and ultra low-dose OC users (20 μg EE).

Long duration of OC use (> 10 years) has been shown to exert a protective effect against uterine fibroids in one study [67] but not in another [68]. In the former study, risk of fibroids was reduced by approximately 17% with each 5 years of OC use, with a 31% risk reduction in women who had used OCs for 10 years (estrogen doses generally $\geq$ 50 μg). In this study, increasing doses of progestogens seemed to provide greater protection. In the latter case-control study, however, OC use less than 10 years since diagnosis of fibroids was associated with little or no reduction. These studies are similar to other conflicting data on the relationship between uterine fibroids and oral OC use [69]. Data to date indicate that OCs provide neither a clear risk of nor protection against fibroids.

The relationship between OC use and endometriosis is similarly conflicting. OCs are used to treat endometriosis, although they seem to alleviate the dysmenorrhea associated with endometriosis rather than eliminate the ectopic endometrial implants. Epidemiologic studies show OC use has been associated with both protection against and induction of endometriosis. Interpretation of study results could be confounded by selection or diagnostic bias, however, because dysmenorrhea and dysfunctional uterine bleeding can be symptoms of endometriosis and can also occur independent of underlying uterine disease. They are also common among perimenopausal women [69].

Epidemiologic studies have consistently demonstrated duration-of-use-related protective effects of OCs against benign breast disease, including chronic cystic disease, fibroadenoma, and breast lumps that have not undergone biopsy. A large multicenter cohort study conducted in the United Kingdom [70] confirmed the findings from 11 previous studies conducted between 1972 and 1979. An additional finding was that reduction in chronic cystic disease was related to the progestogen dose in the OC formulation [70]. This finding supports that reported in a previous prospective survey, in which there was a significant negative association between benign breast disease and dose of progestogen contained in OC formulations [71]. There is recent evidence that OC use may possibly preserve bone mineral density and may decrease the risk of osteoporosis in perimenopausal women. Peak bone mineral density is usually attained around age 25 followed by an age-associated bone loss after age 40 of 1% per year, which accelerates to 3% to 5% per year after menopause [72]. Several studies in postmenopausal

women have evaluated the association between previous OC use and bone mineral density. In a retrospective epidemiologic study, previous OC use was associated with higher levels of bone mineral density measured in the lumbar spine and the forearm [73]. There was also a positive relationship between postmenopausal bone mineral density levels and duration of OC use in a community-based study of osteoporosis [74].

A 2-year longitudinal study was conducted in 81 perimenopausal women to compare the patterns of bone metabolism and vertebral bone mineral density loss among OC users and nonusers [75]. Bone metabolism was evaluated by biochemical markers. OC use during the perimenopausal years prevented the increase in bone turnover and the decrease in bone mineral density of the lumbar spine seen in oligomenorrheic women not receiving OCs. This activation of bone turnover and bone loss is generally seen during the hypoestrogenic oligomenorrheic period of the perimenopause. OC use may be particularly beneficial for women experiencing a prolonged perimenopause.

Although most osteoporosis studies look only at markers, a recent large case-control study in Sweden showed that women taking OCs through their perimenopausal years decreased their risk for a postmenopausal hip fracture by 30% [76].

It has been reported that approximately 85% of perimenopausal women experience some form of hypoestrogenic vasomotor symptoms, such as hot flushes, night sweats, and sleep disturbance [14]. This is the second most common complaint after irregular bleeding. There is evidence, albeit not statistically significant, that OCs reduce the incidence of vasomotor symptoms in these perimenopausal women [77,78].

The OCs may also decrease the occurrence of more severe forms of rheumatoid arthritis. A meta-analysis of results from hospital-based and population-based studies was conducted to determine if OCs have a protective effect on the development of rheumatoid arthritis [79]. When the results of nine independent studies were pooled, the overall incidence of rheumatoid arthritis in ever-use of OCs was statistically significantly decreased. Other studies have concluded that OC use may prevent progression of rheumatoid arthritis to a more severe form by modifying the disease process rather than preventing the initial development of the disease [79]. In a case-control study of women with mild or severe rheumatoid arthritis, there was a significant protective effect of OC use on the course of disease when adjusted for confounding factors [80]. The data also suggested that OC use for 5 years or more might have a protective effect on the development of the disease.

Another common problem to a subset of perimenopausal women is the recurrence of acne vulgaris for similar hormonal reasons that affected them in their early postpuberty years. Many OC regimens that include a progestogen with high androgenic activity may worsen or cause skin problems that are androgen-related in pathology [81]. OC regimens that contain a low androgenic or anti-androgenic progestin, such as norgestimate or drospirenone, however, have been shown to have beneficial effects in women with acne [82,83].

The primary reason OCs may be the contraceptive method of choice for perimenopausal women is their direct effect on the menstrual cycle. Dysmenorrhea is believed to result from a combination of factors, including hyperactivity of the myometrium and uterine ischemia, prostaglandin synthesis and release, pituitary hormones, cervical factors, and uterine neuronal activity [84]. Because circulating levels of estrogen and progesterone also play a role in dysmenorrhea, and ovulation seems to be a physiologic prerequisite for dysmenorrhea, OC-induced anovulation is a therapeutic option for reducing this potentially debilitating disorder [85]. Several controlled studies have shown benefits of OCs for relief of dysmenorrhea [86].

In addition to relief of dysmenorrhea, OCs reduce the duration and amount of menstrual flow, and are considered a primary therapeutic option for women with dysfunctional uterine bleeding patterns [84]. In women receiving low-dose OCs, blood loss and duration of menstruation were significantly reduced after 3 and 6 months of OC use [86]. Because excessive menstrual blood loss has the potential to cause iron-deficiency anemia, by their effect on reducing menstrual flow, OCs may be beneficial in increasing iron stores and decreasing the incidence of iron-deficiency anemia. The motivated perimenopausal woman is also an excellent candidate for using OCs in an extended regimen, shown to reduce significantly bleeding episodes and number of bleeding days [87]. A Dutch study reported that women ages 45 to 49 preferred a cycle regimen that allows for a withdrawal bleed of less than once a month [88]. OC formulations are approved by the Food and Drug Administration and may be used as emergency or postcoital contraception for women of any age at risk for pregnancy. This information needs to be made available to women especially in their perimenopausal years, because contraception may truly have become an afterthought.

The benefits of OC use in perimenopausal women go beyond the realm of those arising from highly effective contraception, such as lowered morbidity and mortality associated with pregnancy, childbirth, and abortion. Coincident with the high contraceptive efficacy of OCs is a potential for improved sexual relationships resulting from a reduced fear of pregnancy and increased sexual spontaneity compared with the use of other contraceptive methods. The potential improvements in quality of life extending from the noncontraceptive medical benefits of OCs are as numerous and varied as the medical benefits themselves. They may be minor, as with achievement of a more regular menstrual cycle, or they may be major, lifesaving, or life-altering benefits, such as avoidance of cancer or reduced risk of osteoporotic fractures. Because long-term use seems to be associated with the greatest noncontraceptive benefits, extending OC use to the perimenopausal woman is logical.

Over the last 10 to 15 years, demonstration of the significant noncontraceptive health benefits of OCs for perimenopausal women has shifted the overall balance of their effects from health risks to health benefits. Patients' lack of knowledge of the many health benefits of OCs, however, significantly curtail their long-term use, and reduce their potential contribution to decreasing morbidity and mortality and to impact public health positively. Surveys conducted in countries around the

world consistently show that most women are unaware of the important non-contraceptive health benefits of OCs [34]. In contrast, the more immediate benefits of relief from acne, more regular menstrual cycles, and less painful menstrual cycles are more commonly recognized [34], which may result from personal experience rather than through patient education.

New options

Perimenopausal women may be very interested in the two new contraceptive delivery systems anticipated in the US market in 2002. The first is the transdermal contraceptive system that delivers contraceptive hormones (ethinyl estradiol and norelgestromin) from a weekly skin patch [89]. The second is a vaginal ring, which delivers contraceptive hormones (ethinyl estradiol and etonorgestrel) transvaginally over a 3-week period of time [90]. These studies have shown efficacy and safety profiles similar to OCs with a higher level of compliance, as expected with methods that do not require daily attention.

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