

Chapter 11- MENOPAUSE AND MENOPAUSAL HORMONE THERAPY

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ABSTRACT

Menopause, defined as twelve months after a woman's final menstrual period, is a natural event that marks the end of spontaneous ovulation and thus reproductive capabilities. In the Western world, the average age of menopause is 51 years.

During the time preceding and following the menopause, many women experience symptoms including hot flashes, vaginal irritation, trouble sleeping, fatigue, and weight gain. Each woman experiences perimenopause uniquely; although menopause symptoms may represent minor inconveniences for some women, other women find these symptoms more disruptive. This period of a woman's life also coincides with the time she is more likely to develop diseases associated with advancing age such as osteoporosis, cardiovascular disease, and cancer.

The clinical use of estrogens to treat menopausal symptoms was first evaluated in the late 1920s. By 1928, the first commercially available injectable estrogen was developed; and by 1942, the first oral formulation of estrogen was marketed. Over the years, data from clinical studies have refined the indications for hormone therapy. For example, estrogen remains the most effective therapy for hot flashes. However, it has also recently been established that estrogen is not appropriate to prevent chronic disease.

Thus, the challenges to clinicians and patients who consider prescribing and using hormone therapy are: whether to treat; with which agent (formulation, dose, delivery method); and for how long.

THE MENOPAUSAL TRANSITION

Early in the menopausal transition (which starts in the late 40s and lasts about 4 years), ovarian estradiol production is erratic and associated with irregular menstrual cycle

length. FSH levels rise in response to a decrease in levels of inhibin, a protein produced by the granulosa cells (1-7). An FSH level > 10 mIU/ml (measured between cycle day 2-5) indicates ovarian aging. As the final menstrual period approaches, estradiol secretion diminishes and finally ceases. Estrone, derived primarily from peripheral aromatization of androstenedione, becomes the predominant circulating estrogen. The postmenopausal ovary does continue to produce androstenedione and testosterone at premenopausal levels (8). The menopausal transition has been more specifically redefined from the early changes in menstrual cycle length and shortening of the cycle to the full postmenopause (9). However no test at the present time will make the diagnosis and the symptom complex remains the best clinical tool.

A variety of symptoms may accompany the menopausal transition (Table 1). While age at menopause ranges from 49-52 years, cigarette smokers can undergo menopause 1-2 years earlier compared to nonsmokers (10).

THE MENOPAUSAL SYNDROME

Estrogen production during natural menopause does not stop abruptly. For five to seven years before the onset of the last menstrual period, ovarian function begins to diminish. Menopause can also be induced surgically (i.e. bilateral oophorectomy) or medically (e.g. chemotherapy or pelvic irradiation). Because

TABLE 1: selected menopause symptoms

Abnormal uterine bleeding
Vasomotor symptoms*
Vulvovaginal dryness, irritation, atrophy*
Urinary incontinence
Trouble sleeping*
Sexual dysfunction
Dyspareunia
Depression
Anxiety
Labile mood
Fatigue
Headache
Myalgias
Arthralgias
Weight gain
Poor memory
Dry skin
Dry eyes
Thinning scalp hair
Hirsutism

ovarian estrogen levels fall abruptly with induced menopause, these women generally experience more severe menopausal symptoms (11, 12). Menopause occurring at or before age 40 is called premature menopause; up to 90% of cases of spontaneous premature menopause (primary ovarian insufficiency) are idiopathic.

After the last menstrual period, the ovary ceases to secrete estradiol. However, smaller amounts of a weaker estrogen, estrone, are still synthesized from androstenedione in the cortex of the adrenal gland and in the interstitial ovarian cells (in minor amounts)(8). Small amounts of this estrone can be transformed into estradiol.

Body mass is directly correlated with the rate of peripheral production of estrone and estradiol in postmenopausal women.

Estrogen synthesis takes place largely in adipose tissue.

Therefore, an obese woman may produce twice as much estrone and estradiol as a thin woman. This may help explain the increased prevalence of hypo-estrogenemic symptoms and the higher risk of osteoporosis observed in thin women.

PIVOTAL STUDIES

The results of the large Women's Health Initiative (WHI) study have been both influential and controversial. In 2002, the estrogen-progestin arm of the WHI was stopped prematurely because of increases in the risk of breast cancer and coronary heart disease (13). In 2004, the estrogen-only arm was also prematurely discontinued, reporting that estrogen therapy had no effect on CHD risk and increased the risk of stroke and deep vein thrombosis in this population(14). Post-hoc analyses suggest no increase in CHD in women starting treatment within 10 years of menopause(15). Other doses and types of estrogens and progestins were not studied in WHI; smaller studies are now underway to further investigate whether age at therapy initiation and different types/doses of estrogens and progestins will result in different health outcomes. Table 2 provides a brief outline of pivotal studies (including ongoing ones) involving perimenopausal women.

The findings of the Women's Health Initiative study, a prospective, randomized trial of more than 16,000 healthy, post-menopausal women, published in July 2002, have thrown the use of HT into question in both the medical and lay communities. The estrogen plus progestin arm of the study was halted because there was a small, increased risk of invasive breast cancer among women receiving the combined therapy, as well as an increased risk of heart attacks, stroke and clotting. These risks were not offset by the benefits: a decrease in colon cancer and hip fractures (13).

However, the average age of the women in the WHI was 63.2 years, and does not reflect normal clinical practice where replacement is used mainly for symptoms, including hot flashes, in women 10 to 30 years younger. Women in the WHI also had an average BMI of 28, one-third had hypertension, and one-half had a history of smoking (66). Thus, at the present time, the relative risk to benefit of using HT in younger, healthier women is largely unknown, and physicians cannot make all clinical decisions based **on** the WHI study, as it appears to apply specifically to the population studied. Hormone replacement is still an important therapeutic modality for women with symptoms and quality of life issues which deserves further study, and should be considered by physicians for their patients on an individual basis. At the present time there is global consensus that women with early or premature menopause should be treated until the normal age of menopause (age 50) and their treatment during these years should not be considered in the calculation of years of postmenopausal therapy(16).

TABLE 2: Important studies involving perimenopausal women

Study	Type	Location	Dates	N	Ages; mean	Hormone formulation
WHI (E+P)	RCT	US	1993-2002	16608	50-79; 63	CE 0.625 mg MPA 2.5 mg <i>Intact uterus. Stopped early after 5.2 yrs (planned for 8); increased CHD events & invasive breast cancer.</i>
WHI (E)	RCT	US	1993-2004	10739	50-79; 63	CE 0.625 mg <i>Status-post hysterectomy. Stopped early after 6.8 yrs; increased risk CVA; lack of CHD benefits.</i>
PEPI	RCT	US	1989-1994	875	45-64; 67	CE 0.625 mg ± MPA 10 mg (days 1-12) ± MPA 2.5 mg QD ± P4 200 mg (days 1-12) <i>Healthy women; 3 years follow-up. HT improved lipoprotein profiles. Unopposed estrogen associated with high rate endometrial hyperplasia.</i>
HERS	RCT	US	1993-1998	2763	67	CE 0.625 mg MPA 2.5 mg <i>Subjects had known CHD. HT 36 months.</i>
NHS	obs				34-59	
SWAN	obs	US	1996-current	3302	42-52	As per patient preference (including no HT) <i>Multiracial, multiethnic (Caucasian, African American, Hispanic, Chinese, Japanese); includes premenopausal; yearly visits—currently tracking 12th-13th visits. Following bone density, cardiovascular health, mood, symptoms.</i>
MWS	obs	UK	1996-current	1084110	50-64; 56	As per patient preference
WISDOM	RCT	UK, Australia, New Zealand	1999-2002	5692	50-69; 63	CE 0.625 mg ± MPA 2.5 or 5 mg <i>Stopped early after median 12 months follow-up (planned 10 yrs) because of WHI results.</i>
ELITE	RCT	US	2004-2013	643	6 yrs vs. 10 yrs postmeno.	E2 1 mg PO <i>2.5 yrs planned; endpoint atherosclerosis by carotid ultrasound.</i>
KEEPS	RCT	US	2005-2012	727	42-58,52	CE 0.45 mg or E2 50 mcg transdermal P4 200 mg (days 1-12)
Harvard Mood	obs	US	1995-2006	460	36-45	No RX
(DOPS)Schierback et al	RCT	Denmark	1990-2008	1006	49.7±2.8	2 mg synthetic 17-β-estradiol for 12 days, 2 mg 17-β-estradiol plus 1 mg norethisterone acetate for 10 days, and 1 mg 17-β-estradiol for six days or 2mg 17β estradiol for hysterectomized

Abbreviations:

WHI, Women's Health Initiative (13, 14).
PEPI, Postmenopausal Estrogen/Progestin Interventions (17).
HERS, Heart and Estrogen/progestin Replacement (18).
NHS, Nurses Health Study(19-22).
SWAN, Study of Women's Health Across the Nation (23-25).
MWS, Million Women Study (26).
WISDOM, Women's International Study of long Duration Estrogen after Menopause (27).
ELITE, Early vs. Late Intervention Trial with Estradiol. (28)
KEEPS, Kronos Early Estrogen Prevention Study.
Harvard Study of Moods and Cycles(29)
DOPS Danish Osteoporosis Prevention Study(30)
RCT, randomized controlled trial.
obs, observational study.
CE, conjugated estrogens.
MPA, medroxyprogesterone acetate.
E2, estradiol.
P4, micronized progesterone.

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However, the average age of the women in the WHI was 63.2 years, and does not reflect normal clinical practice where replacement is used mainly for symptoms, including hot flashes, in women 10 to 30 years younger. Women in the WHI also had an average BMI of 28, one-third had hypertension, and one-half had a history of smoking (66). Thus, at the present time, the relative risk to benefit of using HT in younger, healthier women is largely unknown, and physicians cannot make all clinical decisions based **on** the WHI study, as it appears to apply specifically to the population studied. Hormone replacement is still an important therapeutic modality for women with symptoms and quality of life issues which deserves further study, and should be considered by physicians for their patients on an individual basis. At the present time there is global consensus that women with early or premature menopause should be treated until the normal age of menopause (age 50) and their treatment during these years should not be considered in the calculation of years of postmenopausal therapy(16).

This article will review the current state of knowledge concerning menopause and menopausal hormone therapy (HT). Unless otherwise noted the term HT will be used in this chapter to refer to use of estrogen and a progestogen in women with a uterus and to use of estrogen alone in women who do not have a uterus. The following questions will be addressed: What is the effect of HT on hot flashes, genitourinary tract atrophy, and other symptoms of the menopausal syndrome? Does HT reduce a woman's risk of osteoporosis, cardiovascular disease, or cancer of the breast, endometrium, or colon? Can HT slow the decline of cognitive function and prevent Alzheimer's disease? What recommendations should women be given in light of the Women's Health Initiative findings?

VASOMOTOR SYMPTOMS

A hot flash is a transient feeling of warmth especially over the face and neck, which lasts for several minutes. For some women, hot flashes are associated with drenching sweats, increased heart rate, and post-flash chills. When they occur at night, they can cause sleep disturbances, fatigue, and depression. Vasomotor symptoms typically begin during the menopausal transition, reach maximal frequency and intensity during the two years after menopause, and gradually subside—ultimately lasting 1-5 years. Perhaps 75% of perimenopausal women experience hot flashes (5.) Up to 10% of women experience hot flashes for 10 years or longer. Recent data document vasomotor symptoms for a mean duration of 7.4 years with women starting in the pre or perimenopause having a longer duration (9.4 to 11.8 years) than women starting in the postmenopause (3-4 years). Prevalence of hot flashes differs by culture and ethnicity and can range from 0-80%. African Americans appear to have the longest duration (10.1 years) followed by Hispanics (8.9 years) followed by non-hispanic whites (6.5 years) Chinese (5.4 years) and Japanese the shortest, (4.8 Years) (11, 25, 31-33). Hot flashes occur with greater frequency in women who undergo surgical menopause than in those who experience natural menopause. They are also more common at night, which often results in sleep disturbances, fatigue and depression. Additional factors including warm environments, consumption of alcohol or caffeine, and stress can exacerbate hot flash occurrence. Several studies have documented the effectiveness of estrogen therapy (in various formulations, doses, and delivery methods) for hot flashes (11, 34). For example, the Women's Health, Osteoporosis, Progestin, Estrogen (HOPE) study randomized postmenopausal women to 3 doses of oral conjugated equine estrogens (CEE) 0.625 mg/d, 0.45 mg/d, 0.3 mg/d; with or without medroxyprogesterone acetate (MPA) 2.5 mg/d or 1.5 mg/d. Among the 241 subjects, there was a significant reduction in the number and severity of hot flashes as compared to baseline and placebo after three weeks of hormone therapy (35). Average daily hot flashes fell from nine per day at baseline to two per day after one year of therapy. This reduction was seen in all doses of CEE and CEE/MPA, including the lowest doses (35). In one comparative 12-week trial of 204 postmenopausal women (average age, 52 years), oral CEE 0.625 mg and transdermal estradiol 50 mg/day provided similar symptom relief (36).

SLEEP DISTURBANCES

HT for relief of hot flashes is effective in up to 90% of menopausal women. However, many women still experience sleep disturbances. Poor sleep (including difficulty falling asleep, disrupted sleep, insufficient quantity, and poor quality) affects approximately 45% of perimenopausal women in the U.S. and is associated with reduced productivity, irritability, depression, and cardiovascular disease (37, 38). The causes are multiple and include: hot flashes, nocturia, anxiety, depression, and primary sleep disorders (*i.e.* apnea, periodic limb movements/restless legs syndrome).

Time of night (*i.e.* first vs. second half) appears to influence the etiology of poor sleep. Laboratory sleep studies have shown that hot flashes tend to cause arousals in the first half of the night and are associated with subjective poor sleep. However, apneas and periodic limb movements tend to cause arousals in the second half of the night—a time when rapid eye movement (REM) sleep predominates and suppresses thermoregulatory effector responses like hot flashes. Thus in the second half of the night, primary sleep disorders cause arousals (hence loss of REM sleep) and may subsequently precipitate hot flashes (39, 40).

Determinants of subjective versus objective sleep quality may also be different. Whereas subjective sleep quality tends to be lower in women who experience hot flashes and report anxiety, objective sleep efficiency (ratio of time-asleep to time-spent-in-bed) tends to be lower in women who have apnea or periodic limb movements (40).

Although it is often assumed that complaints of poor sleep are due to hot flashes, treatment of hot flashes may not improve sleep quality if there is an underlying primary sleep disorder or psychiatric condition syndrome. Thus, providers should assess patients for apnea, restless legs, anxiety, and depression, and consider appropriate treatment.

A double-blind, crossover study in hypogonadal postmenopausal women compared the effects of CEE (0.625 mg/d) and placebo on sleep patterns(41). Results showed no relation between hot flashes or night sweats and sleep disturbances. For the women on estrogen, however, sleep quality improved, along with length of REM sleep and sleep latency. The causes of sleep disturbances in the postmenopause are complex and further research is needed.

DEPRESSION

Although prior epidemiologic studies have concluded that postmenopausal women are not at increased risk for depression, studies in the past few years including the Harvard study of Moods and Cycles have shown depressive symptoms are observed more frequently in this during the menopausal transition.(42). Increased psychological distress was seen in the SWAN study of women in the transition (29, 43, 44). This vulnerability occurs even if women do not have a previous history of depression (44, 45), although women with a previous history appear to be at greater risk (46), and depression is more apt to occur in the later stages of perimenopause (47-50). In particular, a subgroup of women who show abnormal mood responses to periods of estrogen withdrawal such as postpartum and premenstrually with a diagnosis of PMDD (premenstrual dysphoric disorder) may be especially vulnerable (51, 52). Women suffering from hot flashes (53) and sleep disorder(54) are also vulnerable, but depressive episodes can occur regardless of the presence of hot flashes(55). Women with early onset of perimenopause also have a significantly increased risk of first onset depression(42, 56) as well as those with a longer length of perimenopause(47, 48). Thus hormonal fluctuations may be a psychological destabilizer and there is some evidence that sex hormones may prevent, attenuate or even treat depressive episodes in the perimenopause (50, 57). This is an area of evolving research, but two independent studies demonstrate successful treatment of depression with transdermal estradiol (49, 58). This treatment; however, does not appear to be successful following menopause (59). Whether asymptomatic postmenopausal women benefit is unproven but the KEEPS study showed improvement in depression, anxiety and sexual function(60). Current recommendations include the use of hormone therapy as well as selective serotonin reuptake inhibitors when treating refractory depression (61). However, the progestin in these patients should be chosen carefully as depressive symptoms may occur with these medications, and some patients cannot tolerate any progestin, even progesterone(62).

With regard to mood, the data supports the theory that symptoms of depression may be alleviated with the use of ET/HT. In a double-blind placebo controlled trial of perimenopausal women, Soares et al found that depressive symptoms were significantly relieved in women receiving estradiol compared to placebo (58). In addition, estrogen has been shown to improve mood in post menopausal women without clinical depression (63, 64). Further research is still needed in this area, but the preliminary data suggest that estrogen may be a possible treatment method for some depression symptoms.

GENITOURINARY TRACT ATROPHY

Large numbers of estrogen receptors are found in the vagina, vulva, urethra, and trigone of the bladder. Thus, atrophy of the genitourinary tract can occur as estrogen levels diminish.

Vulvovaginal atrophy causes significant complaints and is common in the menopause. Symptoms include dryness, dyspareunia, discharge, itching and occasionally bleeding. The symptoms increase with age and may lead to vulvovaginal fissures and stenosis. These symptoms are described as moderate to severe in the majority of women who report them which in one survey was 30%(65).

After menopause, the vaginal walls thin and lose their elasticity. They also produce fewer secretions and lose much of their lubricating ability in response to sexual stimuli. The vulva becomes flattened and thin as a result of the loss of collagen, adipose tissue and the ability to retain water(66). The urethra also becomes thinner and less efficient, with detrusor pressure at the urethral opening decreasing, both during and after voiding. Estrogen deficiency also leads to an increase in fibrosis of the bladder neck, reduced collagen in surrounding tissues, and a decrease in the number and diameter of the muscle fibers in the pelvic floor. There is a decrease in the superficial layer of the vaginal epithelium, a decrease in vaginal secretions and pH (normal is under 4.5) and an increase in vaginal infections due to loss of the normal acidic environment and overgrowth of opportunistic fecal bacteria at the expense of normal lactobacilli. Loss of subcutaneous fat leads shrinkage of the labia and retraction of the urethra(67) Estrogen treatment, both systemic and local can greatly relieve these problems(67-69).

These changes increase a woman's risk of vaginal and urinary tract infection. Atrophic genitourinary tissues are also at increased risk of injury by trauma. Estrogen replacement therapy can significantly lessen these problems. The advantage of using local vaginal therapy is that minimal if any absorption occurs after the first two weeks of therapy, and it can be used without the side effects of systemic therapy. Multiple studies have shown that the absorption of vaginal estrogen therapy is strictly dose dependent and is maximal in the first two weeks of treatment when the vagina is thin and atrophic. With the return of the normal superficial layer of the vagina, serum levels of estradiol remain in the postmenopausal range when used in minimal doses. Studies have followed women for up to 3 months including patients with breast cancer (69-71). Endometrial safety is maintained if the local therapy is minimal (0.5 grams of cream or 10-25ug of the vaginal pill twice a week or the equivalent) but evaluation is warranted for any bleeding(72).

SEXUAL DYSFUNCTION

All of the changes to the genitourinary tract can result in dyspareunia, leading to a decreased interest in sexual intercourse. Fatigue and depression brought on by the vasomotor symptoms and sleep disturbances of menopause can exacerbate this lack of interest in coitus.

Decreased levels of endogenous testosterone, both in women who have undergone surgical menopause, as well as in those who experience natural menopause, may cause decreased libido(73). Women who complain of lack of sex drive may be candidates for androgen replacement, as well as estrogen. In general, androgen levels do not decrease abruptly at menopause but decrease gradually as women age so that decreased libido may be a problem of older postmenopausal women.

OSTEOPOROSIS

The loss of ovarian hormone production after menopause puts women at increased risk for osteoporosis. Without estrogen, osteoclast activity and bone resorption are increased, and bone mass decreases. This reduced skeletal mass and microarchitectural deterioration increase the risk of fracture. At age 50, a Caucasian woman has a 16% lifetime risk of hip fracture, a 15% risk of a Colles' fracture, and a 32% chance of an atraumatic vertebral fracture (74).

Peak bone mass—typically attained by the third decade of life—is determined by genetic and environmental (nutrition, lifestyle, physical activity) factors (75). There is often only slight bone loss between age 30 and the perimenopausal transition (76). The period of accelerated bone loss appears to last approximately 5 years starting 2 years before the final menstrual period lasting until 2-4 years following the final menstrual period. For example, a prospective study of 75 Caucasian women followed for 9.5 years found that subjects lost 10.5% of bone at the lumbar spine over the critical 5-year period while estrogen levels were declining (77).

Although estrogen therapy can prevent bone loss and reduce the risk of fracture in perimenopausal women, it is no longer recommended as first-line therapy for osteoporosis because of the risks associated with hormone therapy and because alternative therapies exist. Studies have shown estrogen to not only prevent bone loss (by decreasing osteoclastic activity), but also to reduce fracture rates by as much as 65%(12). Women in the Women's Health Initiative receiving estrogen plus progestin suffered 5 fewer hip fractures per 10,000 compared to women on placebo (66). Estrogen therapy may be considered in women for whom the alternative agents (e.g. bisphosphonates, raloxifene, teriparatide) are intolerable or contraindicated; in whom estrogen therapy is also indicated for other reasons (e.g., vasomotor symptoms); or in whom the benefits of estrogen therapy outweigh the risks (78). In the WHI, women who received estrogen plus progestin had hazard ratios of 0.66 for hip fractures, 0.66 for vertebral fractures, and 0.77 for fragility fractures at any site, as compared to women on placebo (13). Prophylactic benefit increases when estrogen replacement is begun as soon after menopause as possible. Because bone loss continues as soon as estrogen replacement is stopped, treatment will be needed so as to maintain the positive effects on bone metabolism. However, the longer a woman has been taking estrogen, the more bone she will have when treatment is stopped and bone loss resumes.

While estrogen prevents bone loss in most postmenopausal women, some continue to lose bone mass despite the therapy, presumably because of genetic or environmental factors. Bone density studies should be conducted during the perimenopausal period and then repeated as needed to assess the status of bone loss(79).

All postmenopausal women should have an appropriate calcium intake (up to 1200 mg) and vitamin D (400 IU) supplementation. Concerns about calcium supplements and cardiovascular disease from both observational and randomized studies have changed recommendations, although the issue is controversial(80). Calcium is best obtained from food and women should aim to meet requirements primarily through nutrition and take supplements only if needed to reach RDA .Mean dietary intake of midlife and older women is 700mg/day (81) so supplement in the range of 500mg is appropriate when dietary intake of calcium is low. Recent studies have shown that more than 50% of women over age 50 are vitamin D insufficient and these replacement doses are probably inadequate(82). 1000-2000 IU of Vit D3 are probably a better estimate of replacement. Only 10% of calcium is absorbed when Vitamin D is low. Supplements can help compensate for poor dietary intake of calcium and inefficient vitamin D synthesis. Because calcium carbonate requires acid for absorption, women taking acid-suppressing drugs or with atrophic gastritis should take calcium citrate, which does not require gastric acid for absorption.

CARDIOVASCULAR DISEASE

Cardiovascular disease accounted for 30.7% of deaths in American women in 1999. It surpasses cancer, cerebrovascular disease, lung disorders, infectious disease, diabetes, suicide, and renal disease as the leading cause of death in women today(83). A woman has about 10 times the lifetime risk of dying of ischemic heart disease than of breast cancer, reproductive cancer, or osteoporotic fracture.

An acceleration of heart disease occurs after age 50, and approximately one third of the women who die of cardiovascular disease every year are under 65 years old (more than 100,000). This suggests that menopause (whether surgical, premature, or natural) may be a risk factor for heart disease(84). Because premenopausal women have lower incidences of cardiovascular disease than men and lose this advantage after menopause, it is logical to conclude that estrogen has a cardioprotective effect. It is thought that estrogen deficiency is at least partially responsible for the increased risk of developing heart disease after menopause.

Considerable controversy and confusion has recently erupted over the role of estrogen replacement therapy in preventing cardiovascular disease. A number of trials reported an increased risk of ischemic events when hormone therapy was started in older women with a history of heart disease(21, 85, 86). In response, the American Heart Association recommended that hormone replacement therapy not be used for primary prevention of cardiovascular disease. The results of the estrogen-progestin arm of the WHI showed similar

results. Women on estrogen-progestin therapy suffered 7 more CHD events per 10,000 women than women on placebo. They also suffered 8 more strokes per 10,000 women than those taking placebo(13).

Emerging evidence suggests hormone therapy is most effective in protecting women whose hearts are not yet compromised from future cardiovascular disease as seen in a recent study by Hodis et al.(87). Researchers randomized 222 postmenopausal women with no history of cardiovascular disease, stroke, or cancer who had high levels of LDL (≥ 130 mg/dL) to receive either 1 mg unopposed 17- β estradiol or placebo. After two years, women on estrogen had significantly less thickening of the inner carotid artery wall. Recent data published from the WHI study show that the risk of coronary heart disease is largely dependent on age of the women initiating therapy and the number of years since menopause. The lower risk in the 50 to 59 year age group and in those experiencing menopause within the last 10 years (15, 88) and those on therapy more than 6 years (15). Data on estrogen treatment alone in WHI showed a decrease in coronary calcium, particularly in younger women although the effect was observed in all ages (89). In contrast to these findings, other publications from the same study suggested that the gap between menopause and initiation of therapy has no effect on cardiovascular disease, contradicting their previous report which showed some protection if started early (90, 91). However these observations are from a combination of the randomized and observational studies with most women who were recently menopausal were previously taking hormone therapy. One study showed some protection after 6 years of use(92). Overall, most studies have shown convergence between the observational and the randomized control publications suggesting that younger women starting hormone therapy at menopause are not at increased risk for heart attacks (93). The KEEPS study examined the effects of hormone treatment on surrogate markers of cardiovascular disease in recently menopausal women including carotid intima-media thickness (IMT) and coronary calcium. Carotid IMT increased in a similar fashion in both treated and placebo groups and there was a non-significant trend for less coronary calcium in the hormone arms(94) The DOPS study followed women on hormone therapy for 16 years and although osteoporosis was the primary endpoint, mortality and hospitalizations for both congestive heart failure and MI was reduced in the treated arms. Younger women appeared to show more benefit(30) Probably most convincing are the results of the Elite trial showing that younger recently women treated with hormone therapy showed an attenuation of IMT thickness while women treated who were 10 years past menopause showed no such benefit(95). When women stopped therapy in WHI, the increased risk seen in the treated arm was no longer apparent after a mean of 2.4 years (96). Endothelial dysfunction, not atherosclerosis, appears to be significantly increased in women with hot flashes, perhaps explaining their increased cardiovascular risk profile (97). Since symptomatic women were not studied in WHI, the role of HT in relief of symptoms and in turn of their effect on coronary risk is unclear. An

However, at the present time, HT should not be recommended for the prevention of heart disease.

ALTERED LIPOPROTEIN PROFILES

The increased risk of cardiovascular disease after menopause might be explained by the atherogenic changes in plasma lipoprotein levels associated with estrogen deficiency. At menopause, plasma levels of low-density lipoprotein (LDL) increase by 10% to 15%. According to data from the SWAN study (Study of Women's Health Across the Nation), women experience a very specific increase in lipids at menopause. This includes total cholesterol, low-density lipoprotein cholesterol, and apolipoprotein B. These changes were similar across all ethnic groups (98).

This increase can be prevented with estrogen replacement therapy. Plasma levels of high-density lipoprotein (HDL) increase by 10% to 15% with estrogen therapy and may be an important factor in the cardioprotective effect of estrogen.

The use of progestins, however, in conjunction with estrogen seems to attenuate these beneficial effects on plasma lipoprotein levels to some extent. Data from the Nurses' Health Study showed that women who took estrogen and progestin in combination had the same apparent protection from coronary events as did the women who took estrogen alone(21).

However, as noted previously, the randomized HERS trial showed that HT (with 0.625 mg/d of conjugated equine estrogen and 2.5 mg/d of medroxyprogesterone acetate) increased the risk of coronary events in women with a mean age of 65 who had established cardiovascular disease(18). This effect was noted during the first year of HT use. Following the second year, a progressive protective trend was found with HT, although there was no overall beneficial effect in the study as a whole. Another study examined the effect of HT/ERT as well as ERT in women with angiographically verified coronary disease(99). Again, no benefit was seen. However, these women had proven heart disease and were, on average, 65 years of age. This is considerably older than the age when HT is usually started. These data suggest that HT raised the possibility that started prior to the development of cardiovascular disease might be protective.

Progestins may have variable effects on lipoproteins based on their androgenicity. More androgenic progestins tend to lower HDL levels to a greater degree than do the less androgenic progestins (100). The two types of progestins most commonly used for hormone replacement therapy are those derived from 19-noretestosterone and 17-hydroxyprogesterone. The former are the more androgenic, while the latter have a little androgenicity. Medroxyprogesterone is the most commonly prescribed progestin in the United States and is derived from 17-hydroxyprogesterone.

More recently, micronized progesterone has become available. The Postmenopausal Estrogen/Progestin Interventions Trial (PEPI) showed that micronized progesterone, used with conjugated equine estrogen, had less attenuation of the favorable lipid profile induced by estrogen than medroxyprogesterone acetate (101).

VASODILATION

As important as estrogen's effects on lipid metabolism may be its vasodilatory properties. It appears to potentiate the effects of endothelium-derived relaxing factor (EDRF) in the coronary arteries. It also may affect vasodilation through an endothelium-independent pathway in the peripheral vasculature.

One study looking at postmenopausal women with angina and normal coronary arteries (syndrome X) saw diminished vasodilation before initiation of estrogen therapy and normalized hyperemic response after two months of treatment. Vasodilation was measured by testing hyperemic response to forearm blood flow occlusion. Chest pain either improved markedly, or resolved, in 19 of the 20 subjects. This improvement in angina symptoms suggests that the impaired vasodilatory response to an EDRF/nitric oxide stimulus may be systemic(102).

An additional study reported a beneficial effect for sublingual estradiol in reducing symptoms of exercise-induced myocardial ischemia in postmenopausal women with coronary artery disease(103). These results suggest both a reduction in peripheral vascular resistance and a direct vasodilatory effect in the coronary arteries.

OTHER EFFECTS

Additional studies have found an association between HT and a marked reduction in the pulsatility index of the internal carotid and middle cerebral arteries(104). This finding may help explain the reduction in stroke risk and the improvement in cognitive function seen with estrogen plus progesterone. According to recent data from the Nurses' Health Study, this effect is seen at low doses only (0.3 mg conjugated equine estrogen).

A recent study also looked at the effects of estrogen in women who had recently suffered ischemic stroke or transient ischemic attacks and found no reduced mortality or recurrence prevention with 1.0 mg estradiol compared to placebo(105). These findings discourage the use of HT for secondary stroke prevention.

Other factors associated with estrogen use which could lower the risk for cardiovascular disease include decreases in levels of the proatherosclerotic factor, lipoprotein (a), the procoagulant factor, fibrinogen, and increases in levels of factor 11 (prothrombin). One study showed that with discontinuation of hormone therapy there was a rise in use of antihypertensive medication(106).

BREAST CANCER

One in 8 women will be diagnosed with breast cancer in her lifetime, and risk increases with age(107). In 2001, approximately 40,200 women died of breast cancer, although survival rates have been increasing. The five-year survival rate for women with localized breast cancer has risen from 72% in the 1940s to 97% today. This high survival rate, however, decreases to 77% if the cancer has spread regionally, and to 21% if it has spread distantly(107).

Estrogen, a trophic growth hormone, may promote the growth of preexisting breast cancer. It is still unknown whether it may also induce the growth of new cancers. Use of estrogen alone for at least five years, may be associated with a slightly increased risk of breast cancer according to the Nurses' Health Study. However, a report from the Women's Health Initiative study showed an small increase in breast cancer in women on estrogen plus progestin, women on estrogen only showed no increased incidences of breast cancer compared to women on placebo (13, 14). Recent publications showed a significant decrease in the incidence of breast cancer in this group(108), a surprising finding which may be related to the type of estrogen used in the WHI study (conjugated equine estrogen). The study is ongoing but clarification of this discrepancy has not been forthcoming. The relative risk of the Estrogen plus Progestin (E+P) arm of the study has varied from 1.24 to 1.28 and follow up publication from WHI showed a non significant risk of 1.20 (0.94-1.53)(109). It has been suggested that the effect of E+P is to promote the growth of occult tumors which are present on the initiation of therapy.(110)The risk is very small although the data interpretation has implied otherwise. The absolute number of excess cases is stated as 8/10000 per year and is related to cumulative exposure. Women who had never received hormones in the past in WHI did not have a significant risk over the 5.6 years of the trial and the risk was not significant in younger women.(111)There was no increase in risk for at least 7 years(109)

Many studies have not shown an increased risk of breast cancer with estrogen use. A large meta-analysis of 51 epidemiologic studies (involving more than 160,000 women from 21 countries) showed that HT increases the risk of breast cancer and that risk increases with longer use(112). That is, for every 1,000 women who began using HT at age 50 and continued using it for 5, 10, or 15 years, an additional 2, 6, or 12 cases of breast cancer would be expected to occur. However, another review showed that at doses of 0.625 mg/d conjugated estrogens, there was no increased risk of breast cancer.

Data from the Iowa Women's Health Study showed no increased risk of breast cancer in women who had used HT versus those who had not taken hormones(113). Additionally, when researchers went back and analyzed data from women who had developed breast cancer, they found that HT, in a very small number of women, was associated with cancer with a favorable prognosis(114). This finding is supported by other studies which have shown that women who use HT are less likely to have metastatic disease, and have a longer life expectancy than women who have not used HT(19). The findings of these studies suggest that rather than acting as a carcinogen, estrogen may act as a mitogen. However, one possible explanation for these findings is that women on HT are more likely to be seeing a doctor regularly and to undergo regular breast examinations and mammograms.

Data from the Nurses' Health Study showed a survival advantage for women taking estrogen at the time their breast cancer was diagnosed. The increased survival rate was associated with a lower frequency of late-stage disease and undoubtedly reflects earlier diagnosis in estrogen users(19). However, other evidence suggests that estrogen users develop better differentiated tumors and that surveillance or detection bias is not the only explanation for better survival(115, 116).

A number of recent studies have aroused concern over the effect of menopausal HT on breast tissue density. In women not on HT, breast density has been found to be an independent risk factor for breast cancer(117). Hormone therapy has been found to increase breast density, with the greatest increase in women on conjugated estrogen and progesterone(118).

Although an association between breast density and breast cancer has not been seen in women on HT, there has been some concern that mammograms may be less effective in women on HT with greater breast density. However, Rutter et al. showed that two weeks after discontinuing HT, women's breast density returned to normal(119). Therefore, until this issue is better understood, it may be advisable for women to discontinue HT for two weeks before a mammogram exam, especially in the case of prior problematic mammograms.

Evidence suggests, however, that estrogen plus progestin may have an impact on breast cancer. In July 2002, the estrogen plus progestin arm of the Women's Health Initiative study was stopped due to a small increase in the incidence of breast cancer among women taking this combination. This risk amounted to approximately 8 more women per 10,000 being diagnosed with breast cancer compared to those on placebo(13). It is important to note, however, that the average age of women in this study was 63.2 years and does not reflect women on HT in normal clinical practice. In addition, 50% of the women in WHI were either current or former smokers, they had an average BMI of 28 (well-above normal), and 1/3 suffered from hypertension.

In the MWS (Million Women Study), the large British study, women on HT followed for 2.6 years were found to have an increased risk of breast cancer (RR 1.66) (26). Various hormone preparations were tested in this trial and similar risks were reported for all types, suggesting that risks are not confined to the standard CEE/MPA dose used in WHI. It is important to note though, that women taking estrogen only had a significantly lower increase in risk compared with women taking both an estrogen and progestogen. It is an important to recognize that this was an observational study only and hence has a larger potential area for error.

Although there is some evidence that combination therapy may increase risk of breast cancer above that of estrogen alone, neither a protective, nor a detrimental effect has been demonstrated convincingly, particularly for younger, healthier women. One study interviewed nearly 4000 women with and without breast cancer and found a significant correlation between use of continuous combined replacement therapy and breast cancer(120). However, the risks were higher in thin women than in heavier women which may confound the results. Also, it is possible that the use of cyclic therapy could provide the additional risk, and HT was generally given at higher doses that are rarely used today.

While there has been little consistency among the findings of the various studies on the effects of menopausal HT on breast cancer, one issue that is consistent in the literature is the observation that mortality from breast cancer is decreased among ET/HT users. A summary of the literature from 1990-2001 shows the RR of mortality consistently to be <1.0 with HT use [75-80]. One hypothesis to explain this observation is that HT may promote the development of slow-growing tumors or discourage the development of more aggressive tumors. Hulley et al, reported that tumors in women taking /HT were smaller, had a better histologic differentiation, an a lower cell-proliferation rate compared to nonusers(121). It has also been posited that better screening of these women leads to lower mortality rates.

The argument that menopausal HT should not be given to women who have a personal history of breast cancer may seem reasonable based on evidence that breast cancer is a hormone responsive tumor. However, while women with a first-degree relative (mother, sister, or daughter) who has or had premenopausal breast cancer are at increased risk by virtue of their family history alone, their risk of breast cancer is not thought to be increased further by HT use. Eighty percent of women who develop breast cancer do not have a family history. Sellers et al., examined HT use and breast cancer risk in women with a family history of breast cancer and found no statistically significant increase in risk in past or current users, regardless of duration of use (113). This is supported by the findings of Rebbeck et al., who studied women who were carriers of the BRCA1 gene mutation (122). Bilateral prophylactic oophorectomy was associated with a 47% reduction in breast cancer risk in this population. HT use did not negate the observed reduction in

cancer risk. Interestingly, studies of breast cancer survivors showed that women using HT had a lower risk of recurrence compared to survivors not using HT (123, 124).

Breast cancer incidence is thought to increase after hormone use and since WHI there has been much interest on the role of the progestin in combination with estrogen in contrast to the use of estrogen alone(13, 14, 109). In general most studies that have shown a small increase have shown more of an effect with the combination (26) and nurse health and collaborative study). This has led to speculation as to the role of progestin, and to the minimization of progestin use despite the well-recognized and significant risk of endometrial cancer with the use of unopposed estrogen. Some recent studies suggest the progesterone and dydrogesterone may be safer than other progestins but no randomized studies examine this question(125). In general, some effect is seen with treatment duration and some studies show an effect although small. WHI reported an increase in breast cancer risk in the combined therapy arm in subjects who had used hormones prior to enrollment but only after 5 years (109). A later paper from the WHI study however suggested that the risk was higher in women who initiated therapy soon after menopause (within 3 to 5 years) (90). However, in this study, a much larger group of women who were recently menopausal had been on HT and the effect was more pronounced in the less rigorous observational arm. In general the effect takes several years to appear and is small. When hormones are discontinued the effect starts to decline within one year (96). All of this confusing and contradictory data suggests that the combined HT may be acting as a promoter in susceptible women with undiagnosed subclinical cancer and the promoter effect may disappear with discontinuation of therapy. This may also explain the overall drop in breast cancer seen with the Seer (Surveillance, Epidemiology and End Result) cancer registries database report. This report showed a drop in breast cancer rates after 2002 when women stopped hormone therapy after the WHI publications(126). This effect has not been seen universally and the trend was actually seen prior to the reports. In fact there has been a drop in many different cancer rates, possibly due to earlier detection and earlier treatment(127). Another item of interest is that the use of the less common lobular cancer of the breast (approximately 16 % vs. 70% for more common ductal cancers) is increased with hormone use (128). However this effect was not seen in WHI. Both combined hormone use and estrogen alone lead to denser breasts and more abnormal mammograms (111, 129). This effect is rapidly reversible and stopping hormones 10 to 30 days before a mammography may decrease abnormalities requiring follow up(130). One group of women who benefit from hormone therapy is the women with BRAC 1 and 2 mutations who undergo oophorectomy as prophylaxis. Use of HT does not appear to place them at risk for the genetically determined breast cancer and will improve quality of life(131). It will also prevent the effects of estrogen deprivation at a young age. The effects of stopping hormones are contradictory depending on the study. The Nurse's Health Study reports that the risk is no longer present after 5 years while follow up in The WHI study shows a persistence of effect after 11 years of follow up(132).

Breast cancer prognosis does not appear to be influenced by the high hormone levels during pregnancy, nor has oral contraceptive use been shown to increase breast cancer risk. These observations may allay some of the fear regarding the use of exogenous hormones after menopause

OVARIAN CANCER

Data on ovarian cancer has not shown a consistent risk with use of hormone therapy. There is possible weak association with long term (at least 10 years) of therapy but data are inconclusive for recommendations (133). Its use does not adversely affect the risk of cancer in BRCA mutations (134). While WHI researchers reported an increased risk of ovarian cancer (HR 1.58), it did not

reach statistical significance (135). Other studies too, including HERS and a meta-analysis of 15 case-controlled studies^{found} no significant association(135-137).

ENDOMETRIAL CANCER

In 2001, 38,300 cases of endometrial cancer were diagnosed, and 6,600 women died of the disease. The mean age at diagnosis is 61 years, with most cases occurring in women 50 to 59 years old.

Estrogen alone causes endometrial hyperplasia and a two to three-fold increase in the risk of endometrial cancer. However, the addition of progestogen reduces this risk to lower levels than those seen in women not on HT(138, 139). Thus, the addition of a progestational agent to postmenopausal estrogen therapy is now standard for women with an intact uterus. While there have been some reports that the risk of endometrial cancer may be slightly increased even with the combined therapy, most studies have not confirmed this. Women in the WHI study on combined therapy showed no difference in endometrial cancer rates compared to women on placebo (13). Recent research has focused on the use of lower doses of estrogen and a progestogen in HT to reduce the risk of endometrial cancer(140).

The dose of progestogen given depends on several factors, including the number of days given each month, the amount of estrogen given, the individual needs of the patient, and her ability to tolerate the medication. Side effects of progestogen can include anxiety, irritability, depressed mood, acne, bloating, fluid retention, headaches, breast tenderness, and bleeding problems. The inability to tolerate these effects is the main reason for poor compliance or discontinuation of HT.

COLON CANCER

Despite being one of the major causes of cancer-related mortality in women, colon cancer is often overlooked by patients in their risk assessment of HT. Case-controlled and cohort studies have both found a 50% decrease in relative risk of colon cancer in women who are current or long-term HT users compared to women not on HT. In addition, reports from the WHI study showed that the combined estrogen plus progestin therapy was associated with a decrease in the incidence of colon cancer compared to women on placebo (6 fewer cases per 10,000 women on HT(13). This was not found with estrogen alone(14). Although the exact mechanism of estrogen and progestin's protective effect on the colon is unclear, it has been suggested that estrogen acts to decrease bile acids, which are thought to be carcinogenic. At present; however, although the evidence that HT may be beneficial in reducing the risk of colon cancer should be considered, there is insufficient evidence to warrant recommending long-term HT solely for this purpose.

NEUROLOGIC FUNCTION

Cognition

The existence of estrogen receptors in the hippocampus, a part of the brain essential to learning and memory, has been known for some time. Several mechanisms may account for the effects of estrogen on the brain. Firstly, estrogen increases levels of choline O-acetyl-transferase, the enzyme needed to synthesize acetylcholine, a neurotransmitter thought to be critical for memory(141). Studies on healthy middle-aged and elderly postmenopausal women have supported the theory that estrogen may help to maintain aspects of cognitive function(142),(143). Data also suggest that estrogen therapy may enhance short- and long-term memory(144),(145). Additional effects of estrogen on neural function include: protecting neurons from oxidative stress and glutamate toxicity (146),(147), increasing glucose transport and cerebral blood flow , and stimulating the branching of neurites (148). A recent review of clinical trials of hormone therapy suggest that there is a clear difference between the effects of estrogen therapy and estrogen plus progestin (149). There is modest support for the beneficial effect of estrogen alone on verbal memory in women under 65, and possibly surgically menopausal, while a harmful effect is seen with estrogen plus progestin in women over 65. Conjugated estrogen with medroxyprogesterone acetate may also have some detrimental effect on younger women.

Estrogen alone appears to be neutral in women over 65. Thus the age of initiation of therapy and the use of progestins are important when evaluating possible effects on verbal memory(149). At present there is no combination which appears to be neutral to verbal memory and there is suggestion of some harm even with micronized progesterone (150). Hot flashes appear to relate to memory dysfunction, and some of the cognitive improvement on hormone therapy may relate to the treatment of the hot flashes(151).

Alzheimer's Disease

For every five years after the age of 65, the prevalence of Alzheimer's disease doubles in the population. Nearly 50% of women over the age of 75 may suffer from the condition(152). As the population ages over the next 20 years, these numbers are expected to increase.

According to epidemiologic evidence, there is reason to believe that estrogen deficiency may contribute to Alzheimer's disease. Low body weight is associated with low levels of circulating estrogens in postmenopausal women. Women who suffer from Alzheimer's disease tend to have lower body weights than women without the disorder(153). Incidences of Alzheimer's disease are low or its expression is delayed in postmenopausal women with high levels of endogenous estrogenic steroids or those receiving long-term HT.

One explanation for estrogen's apparent protective effect may involve neurotransmission. Estrogen acts as a trophic factor for cholinergic neurons in vitro. Cholinergic depletion is the most prominent neurotransmitter deficit in Alzheimer's disease.

With regard to the association between risk of Alzheimer's Disease and HT use, however, there is little consistency in the literature. However, while HT does show promise in preventing or delaying the onset of the disease, a recent study showed no benefit of either 0.625 mg/d or 1.25 mg/d of estrogen on Alzheimer's progression(154). Most likely, estrogen may merely delay the deterioration seen in Alzheimer's patients. Paganini-Hill and Henderson(155) reported a 35% decrease in risk for ET users compared to placebo, and Zandi et al.,(156) reported a 41% reduced risk for ever users of HT. However, the results from the WHIMS, the Women's Initiative Memory Study, a substudy of WHI, reported that while HT did not significantly increase the risk of mild cognitive impairment (HR 1.07), it did increase the risk of probable dementia (HR 2.05) (157). The effect of HT on different subtypes of dementia could not be determined because the number of cases was too small. It must be noted, however, that because the WHIMS participants were all 65 or older, these results may not apply to women who initiate HT at a younger age.

The results of the Cache County Study(156) serve to further confuse the issue. In this prospective study of incident dementia in older women (mean age 74.5 years), the risk of AD was increased in current HT users with 10 or fewer years of therapy (HR 2.41 for fewer than 3 years of therapy, 2.12 for 3-10 years). For current users with more than 10 years of therapy the HR was 0.55, indicating a decrease in risk, but this value did not reach statistical significance. Interestingly, in past users, reductions were present in all age groups and showed a duration effect (HR 0.58 for fewer than 3 years, 0.32 for 3-10 years, and 0.17 for more than 10 years).

OTHER POSSIBLE RISKS

Thromboembolic disease

The Nurses' Health Study showed a twofold increase in the risk of pulmonary embolism among postmenopausal women who were current estrogen users. The recent findings of the WHI study confirmed these findings for women on combined estrogen plus progestin therapy. Women on this treatment suffered 8 more pulmonary emboli per 10,000 than women on placebo(13). Although estrogen use has been associated with an increase in the relative risk of venous thromboembolism (VTE), the absolute risk remains low, as VTE occurs infrequently in this setting. Women on combined estrogen-progestin therapy in the WHI study suffered 18 cases of more venous thromboembolism than women on placebo. However, when considered against a

50% reduction in cardiovascular disease risk, the increased risk of VTE does not contraindicate estrogen replacement. It does, however, show that patients should be screened for a history of idiopathic thrombosis as this has been a consistent finding (22).

Gallbladder disease

Some epidemiologic studies have found an increased risk of gallstones among women who use HT. Estrogen has been shown to increase cholesterol saturation of bile, alter bile acid composition, and decrease bile flow. Each of these effects can enhance gallstone formation. Data from the Nurses' Health Study (54,845 postmenopausal women monitored for eight years) showed that current HT users were more likely to have undergone cholecystectomy than nonusers (relative risk, 2.1). This risk tends to increase with long-term therapy and with high doses of estrogen(158).

Weight gain

Because many women gain weight as they age, a common fear is that HT will exacerbate this problem. However, this is unconfirmed by prospective studies. The PEPI trial showed that women on HT gained less weight than women not taking hormones(101). Attention to diet (with reduced fat intake) and regular aerobic exercise for weight maintenance should be recommended to all postmenopausal women. Data from WHI also showed an attenuation of increases in weight seen with age in the combined hormone treated arm(159). This suggests there may be some beneficial effect to HT on the normal increases that are seen in postmenopausal women and that the effect may protect against the increase in central obesity seen in hypoestrogenic menopausal women. A decrease in the incidence of diabetes, and lower insulin levels suggestive of better insulin sensitivity may be related to this attenuated weight gain.(160).

OTHER POSSIBLE BENEFITS

Age-related macular degeneration

About 35% of patients over the age of 75 are affected by macular degeneration, the leading cause of severe vision loss in the elderly. One study showed that women who experienced menopause earlier in life had a 90% increased risk of developing symptoms of age-related macular degeneration later in life as compared to women who underwent menopause at an older age(161). Some studies have shown a small reduction in the incidence of this eye disorder among users of HT(162, 163).

Skin

It is thought that skin may be an important target organ for reproductive hormones. In postmenopausal women, dermal collagen decreases, and skin becomes thinner. Applying estrogen cream to the skin after menopause improves the external appearance of facial skin. In addition, systemic HT increases dermal collagen and limits age-related skin extensibility. To date, of the eleven clinical trials that examined the effect of HT on collagen levels, only one failed to demonstrate efficacy (164). Furthermore, results from a recent study indicates that estrogen also increases skin thickness (165).

HT has also been shown to accelerate cutaneous wound healing, both microscopically and macroscopically, in postmenopausal women (166). This study also showed delayed repair of acute incisional wounds in ovariectomized young female rodents; the delay was reversed by the topical application of estrogen.

Tooth loss

The risk of tooth loss increases after menopause. Osteoporosis, as well as estrogen deficiency, could both be contributing to this effect. Data from the Nurses' Health Study indicate that the risk of tooth loss may be decreased in women with a history of estrogen therapy (167).

TREATMENT

Non hormonal and combination treatments

Several treatments have recently become available and have FDA approval for relief of vasomotor symptoms. This includes a selective serotonin reuptake inhibitor, low dose paroxetine(168, 169) and basedoxifene/conjugated estrogens which also affords protection of bone. The latter consists of a combination of CEE and a SERM and is indicated for women with a uterus. A progestin is not necessary as this combination offers endometrial safety(170-172). Another SERM ospemifene has been approved for the treatment of postmenopausal vulvovaginal atrophy (173-175). Another treatment consists of a Swedish pollen extract femal, which has been shown to be effective in a small study for a composite of menopausal symptoms including vasomotor symptoms, fatigue and quality of life(176).

HORMONE THERAPY PRINCIPLES

Over the years, doses of estrogen in hormone therapy have been decreasing: until the mid-1970s, daily doses of CE as high as 1.25 or 2.5 mg were commonly used. Today, a CE dose of 0.625 mg/day is considered the "standard" dose for estrogen therapy while many women have relief of symptoms with even lower doses.

The goal of hormone therapy is to reduce menopausal symptoms (e.g., vasomotor symptoms, sleep disturbance, vulvovaginal symptoms, decreased libido) using the lowest effective dose for the shortest amount of time. Use of the lowest clinically effective dose of HT for relief of menopause-related symptoms and for prevention of osteoporosis is now recommended. Low-dose estrogen therapy (ET) is currently defined as a dose of oral CEE of ≤ 0.45 mg/d, oral estradiol ≤ 0.5 mg/d, transdermal estradiol ≤ 0.0375 mg/d, or the equivalent. The benefit-risk ratio of hormone therapy for each woman is influenced by the severity of her menopausal symptoms and their impact on quality of life, her current age, age at menopause, time since menopause, cause of menopause, and baseline disease risks. Some patients may require "standard" doses; however, and doses can be reduced if desired after 6 months to a year.

Generally appropriate indications include also treatment or prevention of osteoporosis in women who are not candidates for (or cannot tolerate) other osteoporosis therapies including bisphosphonates or teriparatide.

Absolute contraindications for systemic HT include hormone-related cancer, active liver disease, history of hormone-induced venous thromboembolism, history of pulmonary embolism not caused by trauma, vaginal bleeding of unknown etiology, and pregnancy. Relative contraindications include chronic liver disease, severe hypertriglyceridemia, endometriosis, history of endometrial cancer, history of breast cancer, coronary artery disease.

Guidelines for hormone use are reviewed in the statement of the North American Menopause Society(177) and recently by the Endocrine Society(178).

Considerable confusion has developed as a result of the numerous transdermal preparations which have appeared on the market. The effective dose depends on the delivery rate and the surface area applied so that there is much variation in terms of estradiol delivered to the blood stream. The following charts attempt to present equivalent doses. Lower doses take longer (4-7 weeks) for effective relief, and it is important to individualize therapy. Most preparations take a full 12 weeks for maximum effect although standard therapy provides relief sooner (2-3 weeks). There is also much debate as to the safety of oral vs. transdermal estrogen and the issue of dose vs delivery has not been resolved by double blind randomized trials. One study suggests that venous thromboembolism may be lower with transdermal products, but the doses compared were not equivalent(179). Another study shows a decreased risk of

stroke in women on transdermal preparations with higher doses of both oral and transdermal estrogen showing significant effect (180). One study suggests progesterone may be associated with a lower risk of breast cancer than progestins but this again awaits further study (181).

Bioidentical Hormones.

The unfortunate publicity concerning compounded hormones mislabeled as ‘bioidentical’ has suggested that custom made preparations based on saliva or blood levels were safer or better tolerated has led to a cottage industry which has no scientific basis. These preparations offer no advantage over regulated and tested preparations approved by the FDA, and their risk is equivalent to commercial compounds. Claims that they are safer are misleading particularly since they have not been studied and one of the estrogens used, estriol, has no safety or efficacy data. Prescribers who claim they are more “natural “ do not inform patients that they are synthesized from plant chemicals extracted from yams or soy similar to some commercial preparations.

In general initiation of treatment of the symptomatic newly menopausal women will provide benefit which greatly outweighs risk and provides protection from bone loss. Older women who continue to be symptomatic may. continue treatment preferably with lower doses.

TREATMENT GUIDELINES

Although the decision to treat menopausal women rests on individualized risk vs. benefit for the patient some helpful clinical guidelines are useful for the clinician. In general, hormone treatment is being used for symptoms. These include vasomotor symptoms and vulvovaginal atrophy. There are, however, a variety of symptoms which make up the menopausal syndrome and are not strictly classified as vasomotor or vulvovaginal symptoms and are distressing to the patient and may also be a consideration for treatment(182). These include: mood disorders appearing at the perimenopause and menopause, migraines, severe insomnia, anxiety, difficulty concentrating, memory issues, severe fatigue and somatic symptoms especially joint pains and rarely muscle pain or a generalized crawling feeling on the skin. Some patients can endure two hot flashes a day while others who are in stressful or public jobs cannot. Patients are usually uncomfortable and distressed by more than two hot flashes per day. In particular the patient who wakes at night two or more times and suffers from sleep deprivation is usually in need of treatment. Patients suffering from five to seven hot flashes a day are experiencing moderate to severe symptoms and should be offered treatment. The physician should help the patient make a quality of life decision and advise these patients on the low risks associated with treatment particularly for a few years. Some patients may be experiencing bone loss and hormone therapy is ideal for this type of patient. Some of the estrogens on the market are also approved for prevention of osteoporosis and data shows they are very effective and prevent fractures. A patient on hormone therapy does not need a second drug for prevention of bone loss. If bone loss is occurring on hormone therapy a secondary cause should be searched for such as vitamin D deficiency, over treatment with thyroid hormone or hyperparathyroidism. Patients with mood issue may have problems with progestins and micronized progesterone or a vaginal delivery system may be better tolerated. Estrogens should be started first and a progestin added after a few weeks. Patients with migraines also have special tolerability issues and fluctuations of hormone levels which may be triggering the headaches may persist or be aggravated initially by hormone treatment. A transdermal patch may be the best option and a progestin should be started after a trial of treatment with estrogen. The issue of duration of hormone treatment will arise. Two to five years is usual. The small risk of breast cancer is also important to review with the patient. This risk surfaces after 5 years of use and did not surface at all with estrogen alone therapy after 7 seven years. This interval does not apply to patients with premature menopause

who have been shown to be at risk for osteoporosis and premature heart disease if they are not replaced. All patients need a yearly mammogram and the increase in density can be avoided by stopping hormones for two weeks prior to the mammogram if she can tolerate it. Some patients stay on hormone therapy long term because of mood or other issues or they are in the unfortunate 10 percent who continue to suffer from vasomotor symptoms or cannot tolerate other drugs for osteoporosis. Patients with severe mood issues may require antidepressants. Recent data has shown the efficacy of low doses for vasomotor symptoms and many are available. However the patient with severe symptoms may prefer a standard dose which may be lowered after 6 months when symptoms are well controlled. Lastly, vaginal estrogens are an excellent option for patients with symptoms of vaginal atrophy and do not have the risks associated with systemic use. In particular, recurrent urinary tract infections and or vulvovaginitis are a hallmark of genitourinary estrogen deficiency which can be easily relieved or prevented with the use of vaginal estrogen. Treatment with hormone therapy is very individualized and quality of life may be greatly improved its use. When therapy is discontinued, a return of symptoms is common(183) although generally in a milder form. Unfortunately there is little data to guide the physician but many clinicians slowly taper doses over several months.

When assessing risk vs. benefit for long-term risks, the following conclusions from the WHI should be taken into consideration (13, 14, 88):

Over 1 year, per 10,000 women, estrogen/progestogen treated women had the following observed differences compared to controls:

Estrogen and Progestin

- 7 more CHD Events
- 8 more strokes
- 8 more invasive breast cancers
- 18 more VTEs
- 8 more PEs
- 6 fewer colorectal ca
- 5 fewer hip fractures

Estrogen Alone

- 5 fewer CHD events
- 12 more strokes
- 7 fewer breast cancers
- 7 more VTE
- 3 more PEs
- 1 more colonrectal ca
- 6 fewer hip fractures

- Long term follow up of subjects in WHI after discontinuation of treatment(132):
-

• **Intervention: CEE+MPA RR**

- Breast 1.24, Stroke 1.37, Pulm embolism 1.98
- Colorectal CA 0.62, hip fracture 0.67, diabetes 0.81

• **Post Intervention :CEE + MPA.**

- Breast 1.28 all others attenuated

• **Intervention: CEE RR**

- Stroke 1.35, Hip fracture 0.67, diabetes 0.87

• **Post intervention: CEE RR**

- Breast CA 0.70, under 60 favorable mortality, less MI

• **Overall mortality not affected**

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1. Assess patient's risk and symptoms.	
Risks	Symptoms
Osteoporosis	<ul style="list-style-type: none">• Amenorrhea or missed menstrual periods• Hot flashes or night sweats
Cardiovascular disease	<ul style="list-style-type: none">• Urogenital symptoms• Decreased sex drive, libido
Surgical menopause	<ul style="list-style-type: none">• Insomnia• Dyspareunia
Premature menopause	<ul style="list-style-type: none">• Osteoporotic-related height loss, disability, pain• Depression, mood change
Family history of Alzheimer's disease	<ul style="list-style-type: none">• Headache• Irritability, emotional lability

2. If risk or symptoms are present, screen for HT appropriateness.	
CONTRAINDICATIONS	
Absolute	Relative
Hormone-related cancer or active liver disease	Chronic liver disease
History of hormone-induced thromboembolism	Severe hypertriglyceridemia
History of pulmonary embolism not caused by trauma	Endometriosis
Vaginal bleeding of unknown etiology	History of endometrial cancer
Pregnancy	History of breast cancer Proven coronary heart disease or recent event

3. If not appropriate, consider alternative therapies.
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4. If appropriate for HT, consider the following:			
ESTROGEN ALONE IF UTERUS IS ABSENT OR ESTROGEN-PROGESTOGEN IF UTERUS PRESENT		ESTROGEN/ANDROGEN (E/A) THERAPY	
Risks present for:	Symptoms present:	Risks present for:	Symptoms present:
Osteoporosis	<ul style="list-style-type: none"> Hot flashes or night sweats 	Osteoporosis, not responsive to HT	Symptoms as for ERT and/or: <ul style="list-style-type: none"> Low energy Decreased sex drive, libido Muscle wasting
Cardiovascular disease	<ul style="list-style-type: none"> Urogenital symptoms Osteoporotic-related height loss, disability, pain 		
Surgical menopause	<ul style="list-style-type: none"> Insomnia 		
Premature menopause	<ul style="list-style-type: none"> Headache Irritability, emotional lability Depression, mood change Dyspareunia 		

5. After starting ET therapy, re-evaluate at 3 to 6 months.	
<ul style="list-style-type: none"> If symptoms are controlled, continue HT. If symptoms are not controlled or undesirable side effects are present: 	
Symptoms:	
<ul style="list-style-type: none"> Headaches Breast Pain Urogenital symptoms Irritability, emotional lability 	<ul style="list-style-type: none"> Persistent hot flashes or night sweats Decreased sex drive, libido Fatigue Insomnia Depression, mood change Irritability, emotional lability Headache
Treatment:	

<ul style="list-style-type: none"> • Re-evaluate HT (dose and/or type) • Consider lower dose • Re-evaluate (3-6 months) • If symptoms controlled, continue treatment. • If symptoms not controlled or undesirable side effects persist, consider E/A or alternative therapy or consultation. • Issues of treatment duration will vary with individualized consideration of osteoporosis, dementia, or emerging issues. Breast cancer risk is present and is very small, less than 1/1000 women or less than 0.1%. Lower doses can be considered after symptoms are controlled. Time frame to consider lower doses should be individualized. 	<ul style="list-style-type: none"> •
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6. Hormone Products for Treatment of Menopausal Symptoms

Estrogen Preparations

Doses (standard)	Low dose Therapy
<ul style="list-style-type: none"> • Conjugated (equine and synthetic) estrogens: 0.625, 0.9, 1.25 mg, • Micronized estradiol: 1, 2 mg • Ethinyl estradiol: 5 µg • Estradiol valerate: 2 mg • Piperzaine estrone sulfate: 0.625,1.25, 2.5 mg • Esterified estrogen: 0.625, 1.25, 2mg • estradiol acetate 0.9, 1.8 mg 	<ul style="list-style-type: none"> • Conjugated (equine and synthetic) estrogens: 0.3, 0.45 mg • Micronized estradiol: 0.5mg • Ethinyl estradiol: N/A • Estradiol valerate: N/A • • Piperzaine estrone sulfate: N/A • Estradiol acetate 0.45 mg

Transdermal

<ul style="list-style-type: none"> • E2 patch to deliver 0.05 mg/d 	<ul style="list-style-type: none"> • E2 patch to deliver 0.0375 ,0025,0.014 mg /day
<ul style="list-style-type: none"> • E2 gel 	<ul style="list-style-type: none"> • to deliver 0.035, 0.025, ----- • 0.027,0.0125,0.009,0.003/day
<ul style="list-style-type: none"> • E spray 	<ul style="list-style-type: none"> • To deliver 0.021 mg/day

Vaginal Preparations
<ul style="list-style-type: none"> • Conjugated Estrogen Cream • Estradiol Vaginal Cream • Estradiol Vaginal Tablets 25 or 10µg • Estrogen Vaginal Ring 2 mg
Treatment regimen:
<ul style="list-style-type: none"> • Continuous • Cyclic

Progestin and Progesterone doses and types; The doses are for standard estrogen regimens. Doses can be halved with half doses and must be increased with higher estrogen doses. In general doses of estrogen therapy producing 35 to 60 pg/ml serum levels require standard doses of progestin but little literature is available.
CYCLIC
Medroxyprogesterone acetate: 5-10 mg for days 1-14 of each month Norethindrone acetate: 2.5 mg for days 1-14 of each month Micronized progesterone: 100 mg a.m. and 200 mg p.m. for days 1-14 of each month or 200mg in p.m., 2 hours after a meal
COMBINED (Use half with Half doses)
Medroxyprogesterone acetate: 2.5mg or 5mg daily Micronized progesterone: 100 mg daily in the p.m., 2 hours after a meal
Other
Vaginal progesterone 4% : 6 doses every other day monthly. 45 mg per applicator (not FDA approved for menopausal use)
Levonorgestrel containing IUD 20ug/day release -5 year use (not FDA approved for menopausal use)

Combination EPT products		
Cyclic		
Regimen	Route	Available dose combinations
Conjugated Estrogen+medroxyprogesterone acetate :E alone for 14 days then E+P days 15-28	Oral, once a day	0.625 E+2.5 mg P 0.625 E+5.0 mg P (2 tablets: E and E+P)
COMBINED		

Regimen	Route	Available dose combinations
Conjugated equine estrogens (CEE) + medroxyprogesterone (MPA)	Oral, once per day	0.625 mg CEE + 2.5 mg MPA, 0.625 mg CEE + 5.0 mg MPA, 0.45 or 0.3mg CEE +1.5mg MPA
Ethinyl estradiol (EE) + norethindrone acetate (NA)	Oral, once per day	5 μg EE + 1 mg NA, 2.5 ug EE + 1mg NA
17B-estradiol+norethindrone acetate		1MG E+0.5 MG NA, 0.5 MG E + 0.1MG NA,
17 β -estradiol (E) +drospirenone (P)	Oral, once a day	1 mg E=0.5 mg P
Oral intermittent combined		
Micronized estradiol (E) + norgestimate (N)	Oral, once/day	1 mg E + 0.09 mg NE (3 days on E/3 on E+P)

Transdermal Combinations		
17 β estradiol(E) + norethindrone acetate (P)	One patch twice a week	0.05 mg E +0.25 mg P, 0.05 mg E +0.14 mg P,
17 β estradiol (E)+ levonorgestrel (P)	One patch once a week	0.45 mg E + 0.015 mg P
Micronized estradiol (ME) + norethindrone acetate (NA)	Transdermal patch, replaced every 3-4 days	0.62 mg E + 2.7 mg NA 0.62 mg E + 4.8 mg NA

7. Therapeutic Hints:

- Half doses of estrogen preparation can be used to decrease bleeding and breast tenderness. Recent data show good maintenance of bone with this approach.
- Progestins may add to breast tenderness.
- Moodiness and bloating may be due to progestins. Consider changing progestin, or using a lower dose of HT.
- Consider using a patch in patients with high triglycerides to avoid “first pass” affect through the liver.
- To improve HDL cholesterol use oral preparations. Increases are induced via a first pass mechanism.
- Lower doses of HT/ERT have been found to be bone protective in doses equivalent to CEE 0.3mg.
- Lower doses of HT can control vasomotor symptoms effectively when combined with progestin.
- Lower doses or HT/ERT show favorable lipid profiles and changes are intermediate between standard dose and placebo.
- Expect light bleeding or spotting in the first 3 months of therapy particularly with combined regimens. Abnormal bleedings (not the withdrawal bleeding after the progestin in a cyclic regimen should be evaluated with a pelvi/vaginal sonogram. If the endometrium is greater than 5mm an endometrial biopsy should be done to rule out hyperplasia.

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