Menopause

Hormones, Lifestyle, and Optimizing Aging

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KEYWORDS

• Menopause • Hormone therapy • GSM • Genitourinary syndrome of menopause
• Vasomotor symptoms

KEY POINTS

- The average age of menopause is 51.5 years in the United States. Twenty percent of women have essentially no symptoms, and 20% of women have severe symptoms. One percent of women are menopausal by age 40, and 5% by age 45.
- Classic symptoms include hot flashes (usually early on) and vulvovaginal atrophic symptoms, classically later on. Many women and providers do not recognize atypical symptoms, such as diffuse achiness.
- Hormonal therapy is the most effective intervention for symptomatic relief. Considerable controversy over estrogen usage has occurred over the past 17 years, with major rethinking on the topic over the past 2 years.
- Nonhormonal therapies and topical hormonal therapies are also available for women with symptoms who cannot take or prefer to avoid systemic hormone therapies.

Menopause marks a major transition in women's lives. The definition of menopause, 12 months of amenorrhea (without any other explanations), signifies the end of a woman's reproductive capacity. For many women, this change is liberating, freeing them from anxieties about childbearing, and from pain or discomfort related to their reproductive organs. Some women may view menopause negatively, associating it with aging, which in most Western cultures has significant negative connotations.

However it is viewed, the menopausal transition is accompanied by a multitude of symptoms and health considerations that may affect all women. The introduction of the first hormonal therapy for menopausal symptoms in 1942 forever changed the landscape of menopause. First thought to be a panacea, estrogen by the 1960s was being touted as a vital substance for all women (Dr Robert Wilson's *Feminine Forever*);[1] however, prescriptions for estrogen have gone through substantial shifts over the past 75 years.[1]

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Unfortunately, one of the major milestones in hormone therapy history that occurred in 2002 has radically altered clinicians' and patients' comfort with the use of such therapy. The publication of the first set of results from the Women's Health Initiative (WHI) dramatically changed the hormonal landscape. Since that time, the use of menopausal hormonal therapy has declined 80%.[2] Concomitantly, a recent survey of obstetrics and gynecology residents noted that only 21% of their programs had a formal menopause learning curriculum, with 16% reporting a defined menopause clinic as part of their residency.[3] As a result, in the absence of further education, continuity of care for women transitioning through menopause will be jeopardized.

This article aims to fulfill 2 interrelated purposes. First, the author proposes to fill in considerable background for clinicians who have not received adequate menopausal training, and to update everyone on the current state of menopause management for both symptomatic and asymptomatic women. Second, because multiple recent studies indicate that a careful reexamination and reinterpretation of the WHI analyses is required, the author provides a present day perspective on these findings.

Finally, as a stylistic note, in an attempt to best reach a diverse readership, the author has written the core content for ready accessibility, readability, and direct implementation by clinicians. In the same spirit, the author has provided a streamlined minimalist set of references as critical pointers; these, in turn, provide greater specific range so that more specialized readers can find further depth in topics of interest.

DEFINITIONS

Menopause is defined in the first paragraph of this article. The average age of menopause in the United States is between 51 and 52. One percent of women will be fully menopausal by age 40; 5% will be menopausal by age 45. Most women will be fully finished with menses by age 60. Given the prolongation in women's life expectancies, women will be spending 30% to 40% of their lives postmenopausal (contrast this to the year 1900: the average age at menopause was 48, which was also the average female life expectancy).[4]

The concept and timing of perimenopause is much more difficult to define. Most experts will define it as up to 3 years before the final menstrual period and including the first 2 years after the final period; indeed, it is really a retrospective diagnosis. Women are usually alerted by significant menstrual irregularity, and potentially with all the other symptoms of menopause. Many patients mistakenly believe that once they achieve their last period their symptoms will all resolve; much of our responsibility as clinicians is to educate the patients to have realistic expectations. There is no "test" for perimenopause. Most commonly, practitioners will draw a follicle-stimulating hormone (FSH) and estradiol level; however, although abnormal levels (high FSH and low estradiol) may suggest that the patient is in the perimenopausal transition, they do not certify that the last period has arrived, nor that symptoms are likely to abate soon.

SYMPTOMATOLOGY

One of the greatest challenges to clinicians is that although there are classic "menopause symptoms," there is no classic patient. As we go through the menopause transition, we are also getting older, and there is a significant overlap between symptoms occurring with aging and symptoms related to a loss of estrogen. Several major studies have and are examining the components. Among the classic studies are the Melbourne Midlife Women's Study,[5] and the Penn Ovarian Aging study.[6] By enrolling volunteers in their early 40s who were still menstruating, investigators annually studied participants, querying them on various symptoms (such as hot flashes and arthritic

symptoms) and also asking about menstrual changes, and measuring various hormonal levels.

From these studies, it has become generally accepted that vasomotor symptoms (hot flashes and night sweats), sleep disruption, and vaginal dryness are mostly related to a loss of estrogen. Most other symptoms have at least a significant component related to aging.

The other components that need to be addressed are the psychosocial issues facing women in their 40s and 50s. Many are dealing with children leaving home, or returning; challenges in the work force to women getting older; partner issues, related to work and to the relationship itself; and the ever-increasing burden of taking care of older relatives, including parents and in-laws. For example, a woman complaining of depression may indeed be a woman with a history of depression, which does increase her likelihood of a menopausal recurrence. However, many life stressors may be presenting concomitantly, and a confusing picture may emerge.[1]

SPECIFIC SYMPTOMS

Vasomotor Symptoms

Hot flashes and night sweats are the most commonly recognized menopausal symptoms in the United States. They can start many years before the final menstrual period. Twenty percent of women will experience severe hot flashes, defined as being accompanied by sweating and stopping the woman's activity. Sixty percent of women will have moderate hot flashes, producing sweating but allowing the continuation of their activity. Twenty percent of women have no or minimal hot flashes; their levels of estrogen are comparable to the women with more severe varieties. In studies examining interventions for hot flashes, qualifying women experience 7 or more moderate to severe flashes daily, or 50 a week.[4]

Hot flashes do tend to improve over the course of time; however, 10% to 15% of women are still experiencing moderate to severe symptoms 10 or more years postmenopausal. The mechanism of the hot flash is not totally understood. It is believed that the thermoregulatory zone in the hypothalamus is narrowed with the loss of estrogen, and that estrogen administration helps to widen it. Current research is also looking at receptors of neurokinin-B as being involved with temperature regulation, with chemical inhibition blocking hot flashes.

Hot flashes are seen with different intensity in different populations. In the Study of Women's Health across the Nation (SWAN Study), performed in the United States, women of different ethnicities had significantly different burdens of vasomotor symptoms, with African American women associated with the highest level, followed by white Hispanic and non Hispanic women, followed by women of Asian backgrounds.[7]

Loss of sleep often accompanies night sweats; however, studies are equivocal as to whether a hot flash will awaken a sleeping woman or whether she will wake up spontaneously and then experience the hot flash.

Urogenital Symptoms

Genital dryness tends to occur later on in the menopausal transition. As hot flashes tend to appear earlier and get better over the course of time, vaginal dryness tends to get worse. Originally referred to as vulvovaginal atrophy, these changes are now termed "the genitourinary syndrome of menopause." Many women found the term atrophic as pejorative; and with the term GUSM or GSM, the bladder is appropriately included in symptoms. In Drs Meadow Maze Good and Ellen R. Solomon's article, "Pelvic Floor Disorders," elsewhere in this issue, points out that many women with

pelvic floor disorders think that incontinence and prolapse are a normal consequence of aging.

Vaginal symptoms can include dryness, dyspareunia, and burning. Urinary symptoms can include recurrent urinary tract infections, incontinence, and prolapse.

Urogenital symptoms can be addressed by topical over-the-counter interventions, and topical hormonal therapy. They also may be dealt with by systemic hormonal or selective estrogen receptor modulator (SERM) therapy.[8]

Decrease in Libido

Many women do experience a decrease in libido at the time of menopause. This is one symptom that is truly multifactorial. Dyspareunia contributes to loss of interest in sex for many women; this can be readily dealt with, as described previously. However, there are multiple other factors that potentially contribute. In a practitioner-patient dynamic, an ubiquity question, such as "Many women at the time of menopause have a decrease in libido; is that a problem for you?" can make issues much easier for the woman to bring up. Studies have shown that women feel more comfortable when the provider initiates a discussion of sexual issues with them, and studies have also shown that these are seldom brought up.

There is a very limited choice in potential pharmacologic agents to help increase libido; although testosterone has been shown to be efficacious in such settings, there is no formulation approved by the Food and Drug Administration (FDA) for women in the United States. Flibanserin has been approved for premenopausal women, although there are data showing some efficacy in postmenopausal women. A newer product, bremelanotide, a peptide melanocortin receptor agonist, is currently being reviewed by the FDA for female sexual dysfunction.[9]

Mood Swings, Cognitive Symptoms, and Depression

There is considerable controversy on the prevalence of central nervous system–related symptoms. Many women will complain of some or all of these symptoms, and there is controversy on the role of hormonal therapy in treating them all. As noted previously, exogenous stressors and aging issues also can contribute to these problems.

If a woman has a history of previous depression, the menopause transition can certainly lead to a recurrence of symptoms. It also has been shown that for women suffering from cognitive issues and mood swings, the perimenopausal time frame seems worst for these changes. As women progress further beyond the transition time, these changes seem to resolve. Sleep deprivation can exacerbate any of these symptoms, and therapies to ameliorate sleeping patterns can be very helpful.

Achiness

Women also complain of generalized musculoskeletal achiness. In some populations, this is the major menopausal complaint (eg, in the Philippines). Many women experiencing achiness will present for an annual visit after a full evaluation by a rheumatologist, and with all blood tests indicating no evidence of collagen vascular diseases. A significant percentage of these women will respond to hormonal therapy. This achiness is unrelated to bone loss.

Weight Gain

Most women complain of weight gain in the menopausal transition. Animal studies confirm that the loss of estrogen can contribute to weight gain and fat redistribution, with the tendency to gain weight in the abdominal area. The etiology is complex, in that

many women are less active and lose muscle mass, further complicating an explanation of the weight gain. Women may gain approximately 5 to 8 pounds in the menopausal transition. However, once a woman is fully menopausal, further weight gain attributable to menopause should cease.

Skin and Hair Changes

Most women note significant skin dryness as they enter menopause. Many women also complain about hair loss. Although these are not considered classic menopausal symptoms, many women will opt for systemic therapy to combat these dermatologic issues. Any woman complaining of these symptoms should be evaluated with a thyroid-stimulating hormone evaluation to rule out hypothyroidism.

Asymptomatic Health Considerations Associated with Menopause

Even if a menopausal patient comes in for her annual visit with no complaints, there are still health considerations that require attention. Both cardiovascular disease and bone loss are associated with the loss of estrogen, beyond the risks attendant with regular aging. If a woman is not seeing a primary care physician regularly, she should be assessed for cardiovascular risk factors (family history, weight, diabetes, smoking, and exercise habits, and from her obstetric history, a history of preeclampsia). Find out when her last lipid profile was done, and update if needed. Loss of estrogen has been associated with an elevation of low-density lipoprotein and triglycerides. If investigation indicates problems that would not routinely be handled by a gynecologist, the patient should be referred to a specialist.

Although current guidelines do not recommend a routine bone density when a patient becomes menopausal, routine care should include an assessment for risk factors for bone loss. The risk factors are well-covered by Dr Carolyn J. Crandall's article, "Strong Bones, Strong Body," in on bone health elsewhere in this issue. All women should have a bone density at age 65. Major risk factors include history of previous fractures, family history of osteoporosis, low weight (under 127 pounds), smoking, history of corticosteroid use, and previous history of long periods of amenorrhea. If the patient has 1 or more of these risk factors, it may be appropriate to establish a baseline bone density before age 65.

All women should be apprised of the need for good bone health habits. All women should be counseled on vitamin D and calcium intake (ideally with most calcium being consumed from food sources as opposed to supplements). Most women should be taking at least 800 IU daily of vitamin D. Most women (barring contraindications such as history of certain types of kidney stones) should aim to take in approximately 1200 mg of calcium daily. Weight-bearing exercises should be emphasized. Counseling on smoking cessation should be offered.[8]

MANAGEMENT OF MENOPAUSAL SYMPTOMATOLOGY

This section focuses on management of the major menopausal issues definitively related to the loss of estrogen: namely, vasomotor symptoms and GSM. First, the focus is on nonmedical (nonprescription) interventions, and then guidelines for hormonal interventions, as well as nonhormonal medications, are discussed.

Many basic measures may not be known by patients. Simple advice on layered dressing, for example, wearing a shell underneath a sweater, gives women a bit more control over their environment. Keeping a bedroom cool at night, especially during the first 4 hours of sleep, promotes less disrupted sleep. Cooling pillows may help.

Keeping a dry set of night clothes next to a bed will help her if she gets up soaking in sweat.[1]

Avoiding known hot flash triggers usually helps. Classic triggers include hot beverages, spicy foods, and red wine. More broadly, many women will turn to alcohol to help them sleep; this is usually counterproductive, in that it promotes a more disruptive sleep pattern, and exacerbates hot flashes.

Many women believe that certain herbal products and vitamins may help prevent hot flashes. Very few products have been evaluated by prospective randomized double-blinded studies; and herbal products in the United States vary significantly in components so that large randomized trials across many preparations are very difficult to perform. All trials for hot flash relief show a very large placebo effect of at least 35%. Any study of a product for VMS requires a placebo arm.

The role of soy is controversial. Soy contains weak plant estrogens called isoflavones. There are limited studies that show that soy in the diet may help hot flashes. The effect is modest. However, the central question in the literature is whether soy isoflavones also stimulate breast tissue. Again, the topic is quite controversial. Some in the oncology community think that soy is thus somewhat risky; however, many believe that soy may have SERM-like properties, protecting the breast from stimulation by a more potent estrogen. In general, soy in moderation is reasonable. Nonetheless, if a woman is being monitored for breast disease risk by an oncologist, the woman should inform her treating physician of the degree (if any) of soy use.[8]

Prescription Nonhormonal Therapy

There are 2 current mainstays for nonhormonal therapy for vasomotor symptoms. Selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs) have both been shown to help relieve hot flashes. Small doses, even lower than antidepressant dosing, can be helpful. There is currently 1 SSRI product (paroxetine, 7.5 mg) that is FDA approved for vasomotor symptoms. The use of all others is off-label. Given the potential side-effect profile of SSRIs and SNRIs, namely weight gain and loss of libido, the use of these medications must be monitored closely to maximize benefit while minimizing adverse reactions.

The other nonhormonal (and off-label) option is gabapentin. Again, used in much lower doses than for neurologic indications, it can be effective for hot flash relief. Given the potential side effect of sedation, it is usually prescribed before bed, starting at a small dose; a level of 300 mg is usually tolerated. The other side effect is bloating, which again must be monitored in menopausal women.[8]

Hormonal Therapy

The most comprehensive and up-to-date summary of hormone therapy is the 2017 hormone therapy position statement of the North American Menopause Society (NAMS).[10] We summarize their recommendations based on an extensive review of evidence. Readers are referred to the article in *Menopause*[10] and to references indicated. Most of the international societies have endorsed the NAMS guidelines. “The American College of Obstetricians and Gynecologists supports the value of this clinical document as an educational tool, June 2017.”[10]

The author states, “Hormone therapy [HT] remains the most effective treatment for vasomotor symptoms and genitourinary syndrome of menopause and has been shown to prevent bone loss and fracture. The risks of HT differ depending on type, dose, duration of use, route of administration, timing of initiation, and whether progestogen is used. Treatment should be individualized to identify the most appropriate HT

type, dose, formulation, route of administration, and duration of use, using the best available evidence to maximize the benefits and minimize the risks, with periodic reevaluation of the benefits and risks of continuing or discontinuing HT."[10]

These recommendations are in stark contrast to the original interpretations of the WHI findings, which had 2 arms. In the estrogen/progestin arm, only 1 preparation was investigated, namely oral conjugated estrogens plus medroxyprogesterone acetate, 0.625 mg/2.5 mg. In the estrogen-only arm, for hysterectomized women, only conjugated estrogen 0.625 mg was investigated. Yet when the FDA considered the findings of the WHI, boxed warnings were issued for all women, and stated to pertain to all estrogens and progestogens, and to all doses and routes of administration. The study group for the WHI was woman aged 50 to 79, which in general is not the typical group for whom we initiate hormone therapy. Indeed, the purpose of the WHI was to investigate the question, "Does hormone therapy help prevent coronary artery disease?" The study was never intended to be a study of side effects of hormonal therapy for symptomatic women.[10,11] To reinforce this point, WHI investigator and WHI steering committee member Drs JoAnn Manson and Andrew Kaunitz have noted, "its results are now being used inappropriately in making decisions about treatment for women in their 40s and 50s who have distressing vasomotor symptoms."[12]

BASIC CLINICAL GUIDELINES

Estrogens (Systemic Forms)

Two basic oral estrogens are available in the United States: conjugated estrogens and 17 beta estradiol. The conjugated equine estrogen (CEE) used in the WHI is actually a mixture of more than 10 forms of estrogen. The biological activity of 1 mg of estradiol is approximately equivalent to that of 0.625 mg of CEE. There are no direct comparative studies of estradiol to CEE, including any safety comparisons.

All transdermal forms of estrogen are estradiol; these include patches, gels, and sprays. One vaginal ring (Femring) is available that delivers estradiol in a high enough dosage to achieve systemic levels.

The major contraindications to systemic estrogen in any form are unexplained vaginal bleeding, severe active liver disease, coronary heart disease, previous breast cancer, dementia, personal history of thromboembolic disease, and hypertriglyceridemia. Relative concerns would include reactivation of endometriosis or growth of fibroids. Gall bladder disease is a known side effect of oral estrogen therapy; the risk seems lower with transdermal estrogens. Fluid retention and breast discomfort are the most common annoying side effects.

Women who have had a hysterectomy do not need to take progestogens with their systemic estrogens. The WHI, among many other studies, has shown that after 7.1 years of estrogen-alone therapy there was a nonsignificant decrease in the diagnosis of breast cancer. There are some observational studies that have suggested that in women who take estrogen therapy for more than 10 years, there may be a slight increased risk of being diagnosed with breast cancer; others have not shown such a risk.

The major health risk shown in the WHI with oral estrogens was an increased risk of thromboembolic events. European studies have suggested in observational trials that transdermal estrogens do not increase the risk of thromboembolic events (consistent with bypassing the first pass effect through the liver, and no significant effect on clotting factors.) There are no prospective randomized trials. Vaginal estrogens do not increase the risk of thromboembolic phenomena.[13]

Progestogens

Women who have their uterus in place need to take a progestogen with their systemic estrogen to reduce the risk for development of endometrial hyperplasia or cancer. Traditional synthetic progestins, such as MPA (medroxyprogesterone acetate), norethindrone, and drospirenone are all available in oral forms. Some are available as part of transdermal patch systems. An intrauterine device containing levonorgestrel also can serve to deliver the protective progestin. Micronized natural progesterone (FDA approved) also is available, in both oral and vaginal forms.

Another option available to women is the combination of estrogen with an SERM. The SERM bazedoxifene combined with estrogen, in appropriate dosing, can effectively provide endometrial protection. Use of bazedoxifene may be helpful for women who cannot tolerate progestin side effects. In the United States, bazedoxifene is currently available only with conjugated estrogens in 1 pill and 1 dosage level.

Therapies including progestogens include both daily administration of the progestin, and cyclic regimens. Daily regimens are easy to remember. However, daily regimens are associated with a significant rate of breakthrough bleeding (BTB), and the more proximate to the last menstrual bleed, the greater likelihood of BTB. Many women eventually will achieve reasonably rapid amenorrhea with this regimen. Cyclic progestin usually at least initially produces withdrawal bleeding; but the rate of unscheduled bleeding is lower.

Progestogen therapies can be associated with annoying side effects for your patients. Besides the bleeding issues, progestins can induce mood swings and breast tenderness, with MPA being the most likely to induce side effects and natural progesterone the least.

From a health perspective, the major concerning side effect associated with long-term progestin therapy is a slight increased risk of being diagnosed with breast cancer. In the WHI, after 5.5 years of continuous combined conjugated estrogen and MPA, the hazard ratio of being diagnosed with breast cancer was 1.24 (confidence interval 1.01–1.53). The attributable risk was 8 per 10,000 women per year. This number and the attendant publicity was the primary cause of the rapid decline in use of hormone therapy in the United States. (This attributable risk is actually less than that associated with ingestion of 2 glasses of wine daily.) Of note is that in the 18-year follow-up of the WHI, no increase in mortality was noted from breast cancer.[14]

Indeed, published data on the role of hormone therapy and the risk of ovarian cancer are conflicting.[8] It is not clear if hormone therapy increases risk. The studies that have shown a slight increased risk have been large observational trials, and not randomized controlled trials. The WHI E plus P study did not show any statistically significant increased risk.

In case control studies from Europe, micronized natural progesterone (combined with estrogen) has been shown to have a minimal, if any, risk of breast cancer with long-term therapy. There are no prospective randomized data.[15]

Compounded Hormonal Therapy

After the publication of the WHI, a large industry in compounded “bioidentical hormones” arose. The term bioidentical refers to hormonal therapy that is similar to endogenous hormones 17 beta estradiol and progesterone. Most patients assume that these hormones need to be compounded, and are not available commercially. FDA-approved bioidentical estradiol and progesterone are readily available. Also available only through compounding pharmacies is estriol, which is not approved by

the FDA for any use in the United States. There is a common misconception that estriol is safer for use than estradiol; there are no safety data available. Estriol is a very weak estrogen compared with estradiol.

NAMS strongly recommends that "prescribers should only consider compounded HT [hormone therapy] if women cannot tolerate a government-approved therapy for reasons such as allergies to ingredients or for a dose or formulation not currently available in government-approved therapies."[10] One reason patients believe compounded therapy to be safer than commercially available products is that the compounded products are not mandated to be provided with a patient insert from the FDA; as a consequence, many patients assume these products have no side effects associated with their use.[10] Some women have been led to believe that because there are no large studies on compounded hormones, they are safer than the commercially available hormones. That is untrue.

Many of the providers who prescribe compounded therapy rely on salivary hormonal testing, which has been shown to be "unreliable because of differences in hormone pharmacokinetics and absorption, diurnal variation, and interindividual and intraindividual variability."[10]

Androgen Therapy

Unfortunately, there is no FDA-approved form of testosterone available in dosages appropriate for women. Therefore, if one is prescribing testosterone, one needs to rely on compounding pharmacies.

NAMS recommendations for clinical care from 2014 do address androgen therapy. Women with surgical menopause and primary ovarian insufficiency are known to have significantly lower levels of androgens. They do endorse the use of testosterone in "carefully selected postmenopausal women with female sexual interest/arousal disorder, and no other identified etiology for their sexual problem."[4] However, they do note that long-term risks of androgen therapy in women, particularly regarding cardiovascular disease and breast cancer, are not known. Certain side effects are well known, including facial hair, acne, voice changes, and clitoromegaly, as well as lipid and liver function test abnormalities. They do recommend periodically checking blood testosterone levels even though low levels of testosterone achieved in women are not totally accurate.[4]

Vaginal Therapy

Many women will have tried over-the-counter remedies for GSM before consulting their gynecologist; conversely, many will not be aware of them. As mentioned previously, women often need to be reminded about the availability of both lubricants to be used primarily at the time of intercourse, and longer-acting moisturizers to be used on an ongoing basis. The longer-acting products are usually composed of either a polycarbophil or hyaluronic acid, to draw fluid into the vaginal wall. However, if a patient has had insufficient relief from the over-the-counter regimens, and particularly if she is suffering from urinary issues, she may well need prescription interventions.

Vaginal estrogens are available as creams, vaginal tablets or suppositories, and rings. The creams may be used both internally for vaginal symptoms and externally for vulvar issues. The tablets and rings work well for internal symptoms. When used in appropriate dosages, there is minimal systemic absorption. The vaginal ring is kept in continuously, and needs to be changed every 3 months. The other products are usually initiated with daily therapy for 2 weeks, after which usage is switched to a twice weekly regimen.

There are no data that suggest that women using vaginal estrogen therapy need to use any progestins for endometrial protection. If a woman exhibits vaginal bleeding, she should be evaluated, as any postmenopausal woman should.

More recent introductions to our armamentarium include topical dehydroepiandrosterone (DHEA), called prasterone. It is administered nightly as a vaginal suppository. Mechanism of action is through intracrine metabolism of DHEA in the vaginal cells to both estrogens and androgens, with further local breakdown leading to minimal systemic absorption.[16]

None of the vaginal therapies are associated with any significant systemic absorption; accordingly, both the American College of Obstetricians and Gynecologists (ACOG) and NAMS approved use of these products in breast cancer survivors. However, there are no long-term trials available of use of any products and risk of recurrent disease.[17,18]

Systemic estrogen therapy will alleviate symptoms of GSM for most women; however, approximately 20% may need a vaginal "booster," particularly with low systemic doses.

There is one oral nonestrogen therapy available for GSM. It is the oral SERM ospemifene. Ospemifene blocks estrogen activity in the breast, as do all SERMs; however, at the vagina, ospemifene binds to the estrogen receptors and stimulates moisture. Taken once daily with food, it helps alleviate dyspareunia.

Should Hormonal Therapy Be Prescribed for Prevention of Chronic Diseases?

The WHI was intended as a study to evaluate the use of hormone replacement therapy for prevention of coronary heart disease. For the age range studied, namely women 50 to 79, the WHI demonstrated that it did not prevent coronary heart disease (CHD). The official recommendation of the US Preventive Services Task Force, issued in 2017, for women with and without a uterus, was that they "recommended against the use of HT [hormone therapy] for the primary prevention of chronic conditions in postmenopausal women."[19]

However, the final recommendation statement notes that it does not apply "to women who are considering hormone therapy for the management of menopausal symptoms such as hot flashes and vaginal dryness."[19] From a preventive medicine perspective, "it does not apply to women who have had premature menopause (primary ovarian insufficiency) or surgical menopause." A commentary from the European Menopause and Andropause Society emphasizes the latter group, noting "that premature menopause is associated with an increased risk of osteoporotic fractures, cardiovascular disease, etc."[20]

The NAMS (hormone therapy) position statement notes that women with premature menopause "who require prevention of bone loss are best served with HT [hormone therapy]"[10] rather than "other bone-specific treatments until the average age of menopause."[10] The position statement also notes, "For women with POI [premature ovarian insufficiency] or premature surgical menopause without contraindications, HT is recommended until at least the median age of menopause (52 y) because observational studies suggest that benefits outweigh the risks for effects on bone, heart, cognitions, GSM, sexual function and mood."[10]

Recently there has been an emergent generation of women with premature menopause, namely BRCA-positive women who are undergoing prophylactic bilateral salpingo-oophorectomies in their 30s. In the women who have no cancer diagnosis, also known as "previvors," good observational trials do show that there is no increased risk of cancer diagnoses in these young women given hormonal replacement therapy.[21]

What Is the Current Interpretation of Cardiac Risk Associated with Hormone Therapy?

As noted previously, the WHI was undertaken to ask the question "Does estrogen therapy decrease the risk of cardiovascular disease in women?" Studies started appearing in the 1980s indicating that women who took estrogen therapy for menopausal symptomatology experienced a dramatic reduction in cardiac disease. Typical women initiating therapy were in their 40s and early 50s. Although the WHI did include some early menopausal women as participants, the average age of women in the WHI was 63, typically many years after menopause. Twenty percent of the women in the WHI were aged 70 to 79 on enrollment.[11]

It is this "gap time" that is offered as the most likely explanation of the differences in the cardiac effects noted between the observational studies and the WHI. Much earlier primate studies had suggested such an outcome.[22] One study performed subsequently to investigate this hypothesis in humans was the Early versus Late Intervention Trial with Estradiol (ELITE) trial.[23] The ELITE trial used as a surrogate marker for cardiovascular disease the carotid artery intima-media thickness (CIMT). In women started on hormone therapy less than 6 years after menopause, decreased thickening of the CIMT was shown. However, in women started on hormone therapy 10 years or more after menopause, no such benefit was noted. Other trials have reported similar results.

Currently, most cardiologists believe that hormonal therapy started proximate to menopause is quite safe; however, if a woman is many years postmenopausal, it would be prudent to consult a menopause specialist on potential risks. The HERS trial (Heart and Estrogen/progestin Replacement Study) examined the prophylactic use of hormonal therapy in women with established coronary artery disease. The investigators showed that there were no significant differences between treated and control groups in primary outcome (myocardial infarction or CHD death) or in any secondary cardiovascular outcomes. Indeed, the analyses suggested that in the long-term, the treated women were slightly more likely to have *fewer* adverse cardiac events than were the women in the control group over the study duration. Thus, we readily infer that women already on therapy with cardiovascular disease could continue usage of hormonal therapy.[24]

General Hormonal Therapy Guidelines for Cancer Survivors

With the welcome improvement in all forms of cancer therapies, there are burgeoning numbers of cancer survivors. We have alluded to some of the issues earlier in this article. Both ACOG and NAMS have opined that vaginal hormonal therapy is safe for breast cancer survivors, because of the very minimal systemic absorption from these products. These recommendations are usually applied to nearly all cancer survivors, including gynecologic cancer survivors. Certain cancer survivors, such as rectal cancer survivors, are particularly vulnerable to pelvic scarring from pelvic radiation. Most of these women will benefit from GSM therapy.

Concerning the questions on systemic hormone therapy, many cancers have no estrogen receptors. Women who have had hematological or lung cancers are often excellent candidates for systemic therapy. One consideration that may be helpful is to use a transdermal estrogen preparation, for the observational finding that these formulations are less likely to increase any thromboembolic risk.

Most medical oncologists will not allow their patients with breast cancer to use systemic estrogen therapy. If there is a question on an individual basis, these patients would be best referred to a menopause specialist. However, most patients with

gynecologic cancer are reasonable candidates for hormonal therapy. Even women with stage 1 and 2 endometrial cancers are usually considered reasonable candidates for systemic therapy, although there is not abundant prospective randomized data.[25]

Duration of Therapy

There is no exact formula applicable to all women on how long to continue hormonal therapy. The major cancer risk is the very slight increased risk of breast cancer seen with hormonal therapy for many years. The major chronic disease–related benefit will be ongoing bone protection, which persists as long as your patient continues her hormonal therapy. Cardiovascular protection is currently a hotly debated topic. As noted previously, there should be no arbitrary cutoff points, and current NAMS guidelines promote individualization of care, using the "appropriate dose for the appropriate duration."[10]

PERSPECTIVE AND FUTURE DIRECTIONS

Many women will go through the menopause transition with minimal complaints. Some will suffer significantly, and many women will experience issues that neither they nor their care providers will associate with menopause. Even for those who escape significant symptomatology, much basic physiology is affected by the loss of estrogen. Hopefully the guidance presented in this article will help educate providers and their patients.

The American Geriatrics Society has recently published the Beers Criteria for potentially inappropriate medication use in older adults, in which they state that "systemic estrogen is a high-risk medication because of its carcinogenic potential and lack of cardiovascular protective effects."[26] Sadly, many insurers will then decline to pay for the cost of hormone therapy for their patients older than 65 based on this statement,[26] which then places an undue burden on many women in their later years. However, ACOG has directly addressed this issue in its Committee Opinion 565, issued in 2013 and reaffirmed in 2018. Specifically, ACOG "recommends against routine discontinuation of systemic estrogen at age 65 years," and instead recommends that "as with younger women, use of HT [hormone therapy] and ET [estrogen therapy] should be individualized based on each woman's risk benefit ratio and clinical presentation."[27] We strongly recommend that the ACOG guidelines be very actively disseminated to insurers, through multiple media and with political pressure, if necessary, to ensure as best as possible, that women have ready access to hormone therapy and estrogen therapy if and when these therapies are required.

In the spirit of optimizing aging, a critically important recommendation for women is not strictly medical: it is the development of a long-term relationship with a fixed provider or group. With the proliferation of health-related propaganda on the Internet, quality-of-life issues need to be discussed with a longstanding and trusted provider.

We can never cease to reinforce the importance of a healthy lifestyle, with proper exercise and nutrition, independent of any pharmacologic advancements. To augment this point somewhat, many recent studies also have established the utility of some strength training as part of one's workout or exercise regimen, for improvement in both long-term cognitive capability and adverse event protection.

As we indicated earlier, the present extent of menopausal education to providers in training is quite inadequate. Accordingly, the development of educational tools and modules is acutely needed, as is enhanced training. Moreover, a delineation of the symptomatology and efficacy of treatment modalities among racial, ethnic, and sexual orientation subgroups is sorely needed, and quite timely.

As a final and overarching viewpoint, the decision of whether and how to use hormonal therapy is truly a paradigm example of the modern terminology of "shared decision making." Science is evolving, and as our patients are living longer, we can all help them to lead healthier and happier lives.

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