Excerpted from A Modern Practitioner's Guide to the Perimenopause and Menopause. Minkin MJ. Manuscript in preparation.

INTRODUCTION

Why is a menopause guide more relevant now than ever before? In 1900, the average age at menopause in the United States equaled the average female life expectancy: 48. By 2000, while the average age at menopause had climbed to 51.4 years, the average life expectancy for women who had reached menopause was well into the 80's. Yes, there were menopausal women in the world in 1900; the dowager photos of Queen Victoria are illustrative. But we know that women of her era would never have been permitted to discuss their symptoms.

Medical therapies for climacteric symptoms have been promoted for centuries. Hormonal therapies were introduced in 1938. The original drug, Premarin, is still marketed today. Prescriptions have in general risen over the decades, with a few transient declines, until the publication of the first results of the Women's Health Initiative in 2002. In early 2002, 28% of menopausal women were using hormone therapy; by 2004, that number fell to 12%.

Nonetheless, women continue to have menopausal symptoms. Women continue to experience increased risks of bone loss and cardiovascular disease after their final menses. Researchers have yet to find an alternative to hormone therapy with equal efficacy for symptom relief.

This chapter will introduce you to some of these issues.

Age at menopause

The average age in the United States is 51.4 years. Virtually all women will become menopausal between the ages of 35 and 60, with 1% of women becoming menopausal by age 40. The old beliefs about prediction claimed that early menarche would lead to a later menopause (presuming more robust ovarian function); however, demographic studies have shown a very small association here. Family history generally provides a greater degree of predictability for the timing of menopausal onset.

Unfortunately, the symptoms women experience in the early menopausal transition mimic many other medical conditions, and symptomatic women in their 30's seldom initially present to their gynecologists for evaluation. Often, primary care physicians and psychiatrists who deal with these women are baffled by their complaints.

STRAW criteria

In 2001, the **St**ages of **R**eproductive **A**ging **W**orkshop, sponsored by the North American Menopause Society, among other groups, developed a standard nomenclature for the reproductive continuum,

denoted as the **STRAW** criteria. Defining the final menstrual period as stage 0, they defined the early menopause transition as a time of variable cycle length, >7 days different from normal. The late menopause transition was characterized by two or more skipped cycles and an interval of amenorrhea of 60 or more days. Post menopause was divided into an early phase consisting of the first 5 years, with the subsequent years designated as late postmenopause.

Symptoms

Considerable debate surrounds the certification of those symptoms that are classically caused by menopause versus other symptoms that may be more related to simple aging. All experts agree that vasomotor symptoms, including hot flashes and night sweats, are related to menopause. All agree that vaginal dryness is a sequela of menopause. Most will agree that sleep disruption accompanies menopause. Irregular menses, both greater frequency and spacing out, and changes in flow, usually accompany some of these symptoms during the menopausal transition.

Further symptoms, such as irritability, depression, achiness, skin changes, including dryness and hair loss, weight gain, and loss of libido, are sometimes attributed to menopause. Other practitioners may ascribe them to simple aging. Many strategies can be applied to help women deal with all of these issues.

Melbourne Women's Midlife Health Study

In this significant 9-year prospective, observational Australian study, the investigators followed a cohort of menstruating women aged 45-55 years at baseline.* The women were followed regularly as they aged, surveyed for menstrual changes, health issues, symptoms, and blood and urine chemistries, including hormonal levels. As the women went through menopause at different ages, the authors identified those symptoms or complaints that corresponded to aging, and those that developed with loss of estrogen. The symptoms identified as most specifically related to the hormonal changes of the menopausal transition were vasomotor symptoms, insomnia, vaginal dryness, and breast tenderness. Depressed mood was increased by symptoms and by stressors occurring during the transition; sexual functioning was reported to significantly deteriorate with the menopausal transition and aging, although relational factors produced major effects. These findings reinforce the delineation of menopausal symptomatology provided immediately above.

* Guthrie JR, Dennerstein L, Taffe JR, Lehert P, Burger HG. The menopausal transition: a 9-year prospective population-based study. The Melbourne Women's Midlife Health Project. *Climacteric.* 2004;**7**(4): 375-89.

PERIMENOPAUSE

Menstrual irregularities

A few women will have regular menses, on schedule, and then will abruptly cease having periods beyond their last regular cycle. However, the other 90^{+}% of women will experience menstrual irregularities. Most women understand that childbearing potential decreases with age, and that fertility beyond the mid 40's is unusual (although caregivers need to emphasize that childbearing potential exists until a woman goes one year without a period; contraception needs to be continued until that point.) It is easy to explain to women that the menstrual irregularities they experience -- periods closer together, or periods farther apart, and heavier flow -- are related to their decreasing and irregular production of progesterone produced with ovulation, which accompanies their diminishing fertility.

Although our primary differential diagnosis is that most menstrual irregularities are related to the loss of hormonal regulation, we nevertheless need to rule out endometrial pathology, which increases with age as well. Particularly in high-risk patients (such as metabolic syndrome patients), endometrial surveillance with ultrasound or biopsy is recommended before therapy.

Hot flashes, night sweats and sleep disturbances

Although there has been extensive research on this topic, the exact etiology of hot flashes has yet to be firmly established. At the extremes, 20% of women experience no vasomotor symptoms, whereas in sharp contrast, 20% of women have symptoms severe enough to significantly impact their daily activities. However, both groups of women have similarly low estradiol levels and elevated FSH levels. Many researchers believe that hot flashes are worst during the perimenopausal transition, with significant fluctuations in FSH and estradiol levels. The frequency and severity of hot flashes tend to lessen over time, with 85% of women 10 years or more after their last menstrual periods experiencing minimal or no symptomatology. Finally, estradiol levels continue to decline for the large majority of women.

Leading explanations for the onset of hot flashes include a narrowing of the set point for temperature control.** Peripherally, with the hot flash, women develop vasodilation, with local increases in blood flow, and subsequent loss of heat and shivering.

** Freedman RR. Pathophysiology and treatment of menopausal hot flashes. *Semin Reprod Med* 2005; **23**(2): 117-25.

Obese women tend to have more hot flashes than slimmer women. It is generally believed that these women are more insulated and have difficulty dissipating centrally generated heat. Additionally, smokers not only enter menopause 1-2 years earlier than non smokers, but they also tend to have more severe hot flashes.

The SWAN study (Study of Women Across the Nation), which followed women of many ethnicities in the United States throughout the menopause transition, showed that African-American women tend to have more debilitating hot flashes than do Caucasian women, with women of Japanese ancestry suffering the least from vasomotor symptoms.***

*** Thurston RC, Joffe H. Vasomotor symtoms and menopause: findings from the Study of Women's Health across the Nation. *Obstet Gynecol Clin North Am*. 2011; **38**(3): 489-501.

Night sweats can be especially bothersome to some women. Considerable controversy exists as to whether the hot flash first awakens the woman, or conversely, whether the woman awakens first, then experiences the hot flash. Independent of the sequence of events, patients often have difficulty reinitiating sleep.

Sleep disturbances accompany several other medical conditions. One of the more difficult diagnoses is the differentiation between menopause and depression. A useful and primary distinction between these two conditions is that depressed women classically experience more difficulty falling asleep and early morning awakening. In contrast, menopausal women are usually quite fatigued, and have minimal difficulty falling asleep; however, they often wake in the early morning hours, between midnight and 3 AM, and have trouble falling back to sleep.

Vulvovaginal symptoms

During the perimenopause, vasomotor symptoms tend to improve over the course of time, as noted above -- within 10 years of the last menstrual period, 85% of women will exhibit very minimal or no hot flashes. However, as counterpoint, complaints related to vulvovaginal atrophy may start in the perimenopausal transition, and the majority of women will show atrophy on exam within 10 years of menopause.

Studies show that although many menopausal women have some symptoms related to atrophy, women are frequently too embarrassed to discuss them with health care providers. Practitioners often need to initiate the conversation, as patients are reticent to bring up issues involving sexuality and the genitalia. Practitioners therefore must reassure patients that these symptoms are both common and readily and safely treated. When the health care provider initiates the conversation, it legitimizes the woman's complaints.

Additionally, some patients and practitioners assume that only sexually active women will have complaints related to atrophy. Indeed, many women can have discomfort related to daily activities such as walking or biking.

Atrophy can occasionally lead to an increased risk of vaginitis. Decreasing amounts of glycogen in the vaginal mucosa can lead to an increased vaginal pH, as well as decreased colonization of the vaginal by lactobacilli.

Urinary tract symptoms

Most of these urinary tract symptoms are linked to vulvovaginal atrophy. As noted above, changes in vaginal flora can lead to an increased exposure to potential urinary tract pathogens.

Many women have discomfort directly relating to alterations in the bladder and urethral mucosa. Explaining to a patient that her urinary tract tissue has estrogen receptors which are quite similar to her vaginal tissue makes these symptoms more comprehensible to her.

In addition to infections, symptoms of pelvic relaxation, including incontinence, occur more often post-menopausally. Hormonal therapy can serve as a valuable adjunct to surgical and pharmacological interventions.

Achiness

When discussing the complaint of perimenopausal achiness, practitioners may assume that this symptom suggests possible related bone loss, which is also recognized to accompany the menopausal transition. However, the achiness that some women experience can occur in women with totally normal and minimally changing bone mineral densities. We do not know the cause; we assume that part of it is related to dryness changes in synovial surfaces. Some women also seem to have some muscular complaints as well. The typical patient with this complaint will often state that she has seen her primary care giver, or perhaps even a rheumatologic specialist, for evaluation of arthritis; extensive workups usually are non revelatory. Symptoms often resolve with hormonal therapy.

These symptoms also have varied ethnic occurrences. In the Philippines, achiness is the primary complaint of menopausal women, significantly exceeding hot flashes.

Headaches

Women are more prone to migraines than men. Although migraines can occur sporadically, women often describe perimenstrual migraines. During the normal menstrual cycle, estradiol levels fall precipitously just before a period. It is presumed that this fall leads to vascular instability, leading to the migraine. This change can become even more symptomatic in the perimenopausal transition. Perimenstrual therapy with estrogen can relieve this type of migraine.

For some migraineurs, the loss of cycling ameliorates their headache pattern; for some, the perimenopausal transition can be very challenging because of the hormonal fluctuations triggering migraines. If a woman is using estrogen therapy, she often needs to vary doses, trying both lower and higher levels empirically to see which improve symptoms.

Skin changes

Most menopausal women will note changes in skin moisture, (even) apart from vulvovaginal dryness. Considerable data supports these observations; however, dryness is not an official indication for hormonal therapy. Many women find the addition of topical lubricants to be helpful.

Furthermore, some women do note hair loss around the time of menopause. Hair loss may well be related to other aging changes, as well as disease states such as hypothyroidism. Causes other than menopause should be ruled out. Practitioners occasionally use empirical hormone therapy when no other etiology is discovered.

Weight changes

Weight gain is among the most contested of menopausal symptoms: Is it related to the loss of estrogen, or is it simply a function of aging, including decreasing muscle mass? Most authors who note a weight change describe a gain of 5-8 pounds in the menopausal transition; weight tends to stabilize beyond that time frame. If a patient comes in complaining of gaining 30 pounds as a function of menopause, you can assure her that this amount of weight gain is almost never seen simply as a consequence of declining hormones, and you should evaluate her metabolically. This evaluation should also be accompanied by an offer of considerable counseling on nutrition and exercise.

Many menopausal women will tell you that they are quite "active." A simple intervention is to have them use a pedometer or a "FitBit", and have them document exactly how much activity they are regularly doing. A very straightforward recommendation is to encourage them to walk 10,000 steps a day. Strength training is another valuable adjunct. With age, women lose muscle mass; maintenance of muscle mass will increase mobility, and also aid in weight stability.

As noted above, obese women have more difficulty with vasomotor symptoms, so that weight loss is not only beneficial for their medical health, but also, they will feel better as a consequence.

THERAPY -- exclusively Perimenopausal

Bleeding

In women who need intervention whose complaints are solely related to heavy menstrual bleeding, insertion of a progestin coated IUD often alleviates the bleeding, and will provide contraception. Alternatively, women who have completed childbearing can elect to have an endometrial ablation, which usually succeeds in controlling the bleeding. However, in this setting, the women will still need to use contraception until they have become fully menopausal.

If the woman is dealing with other symptoms, oral contraceptive therapy is usually helpful, if the woman is a healthy candidate (non smoker, no significant cardiovascular disease; if hypertensive, well controlled.) Low dose oral contraceptives will usually regulate her menses, obliterate her fluctuating ovarian hormonal production, and provide a fixed daily dose of estrogen and progestin. This will serve to minimize other symptoms, such as hot flashes and sleep disorders.

We try to use 20 microgram ethinyl estradiol pills for symptom relief when possible. Some women, particularly those with heavy bleeding, will require a 30 microgram pill to control bleeding. Many

women will prefer long cycle regulation to minimize days off of oral contraceptives. Many women will benefit by estrogen therapy on "placebo days" if using cyclical therapy, to minimize vasomotor symptoms, as well as estrogen withdrawal headaches. Continuous pill use can be helpful, if they do not experience excessive breakthrough bleeding.

Patients can be reassured that there is no data linking oral contraceptive use to an increased risk of breast cancer. Oral contraceptives also decrease the risk of ovarian cancer and endometrial cancer.

Finally, since menstrual symptoms will resolve with full menopause, we try to avoid hysterectomy, unless we cannot control menses by any other means.

Transitioning off of oral contraceptives

Why transition?: Most women do not understand that even the lowest dose birth control pill contains significantly more estrogen that standard doses of hormonal therapy. 5 micrograms of ethinyl estradiol hormonally acts like 1 mg of oral 17 beta estradiol, so a 20 microgram pill is thus as potent as 4 mg of oral estradiol. The point is that we can usually control menopausal symptoms with 1 mg of 17 beta estradiol.

When to start the transition: There is no one answer. Some health care providers will stop at age 50, and see if the patient resumes menstrual function, or develops menopausal symptoms. Some will use family history as a guide: if all women in the family were in their early 40's at menopause, they will stop pills early; in contrast, if women in the family go through menopause in their late 50's, they will wait until that time to check. Some providers advocate waiting until a woman is 55 to check, working on the premise that the significant majority of women will be menopausal at that point.

How to transition: We routinely recommend stopping birth control pills in the cooler months. If the woman is going to develop hot flashes, she will be less uncomfortable with them in November, compared to July. If after 4-6 weeks she does not spontaneously get a menstrual period, you can obtain FSH and estradiol levels. If she is not menopausal, she can reinstitute oral contraceptives; if she is well into the menopausal range, and symptomatic, she may initiate hormone therapy.

THERAPY – both Perimenopausal and Menopausal

The most effective therapy for all menopausal complaints is estrogen. However, many women are anxious about initiating hormonal therapy, so we will outline an approach that has worked well for this author.

Lifestyle changes

Many women will have figured these out on their own, or will have instituted them based on articles they have read to alleviate menopausal symptoms. But some have not, and you should enquire.

Layered clothing allows the patient to modestly deal with her own inner thermostat -- she can remove external garments as she heats up. “Wick-away” technology may help her to dress more comfortably, as well.

At night, she should keep the thermostat down. If she sleeps with a partner, they should have a dual control electric blanket. She should keep a dry nightgown next to her, so that if she wakes up drenched in sweat, she can change, and get right back to bed. Cooling pillows are another option.

She should avoid known triggers to hot flashes, or at least recognize that what she is taking in may promote symptoms. Most women can figure out their known triggers; common ones include red wine, hot coffee, and spicy foods.

Over the counter/herbals and botanical approaches

Herbal approaches have been used for centuries for “female complaints.” Some have at least plausible explanations of why they make work for hot flashes; others have been traditionally noted to work. Remember that all studies (including those of hormone therapy) on relief of hot flashes have shown considerable placebo effect, up to 50% in some studies. Therefore, for a particular remedy to be validated as effective, it needs to have a placebo control, showing greater efficacy than the placebo in this group of patients.

Some foods have been shown to reduce hot flashes (most notably soy); however, extracts from this food may not work nearly as well as the intact plant. Processing and eliminating potentially beneficial components can reduce efficacy.

In the United States, compared to some European countries, herbal extracts are not treated with the same rigor as pharmaceuticals, by governmental agencies. Products often are not standardized, and manufacturing sites are not routinely inspected. A useful source of information about herbal products is the American Botanical Council. A recent article entitled Exploring the Peripatetic Maze of Black Cohosh Adulterants, by Steven Foster, is available as part of the ABC-AHP-NCNPR Botanical Adulterants Program at Herbalgram, 2013: 98: 32-51.

I often suggest to patients that the most effective of all complementary approaches are soy and black cohosh; if a patient wishes to try these, and has not yet done so, I suggest that she give them a three month trial. If she does not achieve satisfactory relief for her symptoms, she should then let me know, so that we can discuss medical options.

Vulvovaginal symptoms

Above, while discussing the perimenopause, we initiated a discussion of vulvovaginal symptomatology. Here, we continue this discussion with more depth and generality, which is most appropriate since these symptoms are generally more problematic during the menopause and postmenopausally.

For some women, atrophic symptoms are the most bothersome. The downside is that these often get worse over the course of time; however, they are straightforward to treat.

Many women just need reassurance that use of lubricants for intercourse is quite safe and appropriate. Topical lubricants are available over the counter; we recommend water based lubricants, and advise our patients to purchase those without potential irritants, such as perfumes.

For other women, a lubricant is not sufficient, and they require a long acting moisturizer. A polycarbophil product, such as Replens, is available over the counter. Ideally inserted about three times a week, these moisturizers will help with dyspareunia, with ongoing relief.

Vaginal estrogens are safe for almost all patients. Systemic absorption is minimal, and vaginal and vulvar applications will relieve most genital symptoms. Vaginal estrogens do penetrate into adjacent tissues of the bladder and urethra, and can provide relief for many women with chronic postmenopausal cystitis and urethritis.

Vaginal estrogens are safe, and quite useful, in the therapy of women who had had gynecological malignancies, particularly those involving local radiation therapy and possible scarring of the vagina. We also use them regularly in breast cancer survivors, as the systemic absorption is minimal. However, some breast oncologists are anxious regarding such usage, so we encourage our survivor patients to discuss this option with their breast oncologist.

Vaginal estrogens come in three forms: vaginal creams, tablets, and rings. All vaginal estrogens carry the same package inserts as systemic estrogens; you can reassure your patients that vaginal absorption is minimal; nonetheless, the manufacturers must include systemic warnings. A committee from the North American Menopause Society has petitioned the FDA to remove the systemic warnings from vaginal estrogen therapy. Action from the FDA is pending.

Estrogen cream

Several brands are available. Exact recommendations vary, but most physicians recommend inserting 0.5 to 1 gram of estrogen cream intravaginally before bed, several times a week for approximately two weeks, until the vagina is well estrogenized. Maintenance of moisture can usually be obtained by an ongoing twice weekly insertion of cream.

For vulvar dryness, the woman can apply a light coating of cream with her finger to affected areas, following the same timing protocol.

Vaginal tablets

Some women will find the vaginal creams messy, and prefer a prepackaged vaginal estrogen tablet. The tablet can be inserted nightly, or every other night, for two weeks, to achieve good moisturization; again, maintenance is usually achieved through twice weekly therapy.

Some patients will have both a vaginal and vulvar or introital complaint of atrophy; for these women, insertion of the vaginal tablet and digital application of estrogen creams to the affected areas will be helpful.

Rings

Some women will find regular vaginal application of estrogen to be cumbersome, and prefer an ongoing therapy that they do not have to insert regularly. For these women, a vaginal estrogen ring will work well. To describe rings to your patients, you can tell them that they resemble the rim part of a contraceptive diaphragm, but without the cup. The advantage to rings is that they can be inserted by the woman into her vagina, and she can leave the ring there for three months. There has been no association between these rings and either toxic shock or vaginitis.

There are two basic rings: one which has a relatively small amount of estrogen, so that it constantly releases a small amount of estrogen constantly. Marketed as the Estring, it delivers almost no systemic estrogen, and is used exclusively for alleviation of atrophic symptoms. It is designed to be changed every three months. Because of its minimal systemic absorption, no concomitant progestin therapy is required for women with a uterus.

The Femring contains a much higher amount of estrogen, and delivers therapeutic estrogen levels to the bloodstream. It serves not only to moisturize the vagina, but it also is used for alleviation of vasomotor symptoms and prevention of osteoporosis. For women with a uterus, progestin therapy should be added to protect the endometrium.

Ospemifene

In 2013 the first oral non estrogen therapy for symptomatic vulvovaginal atrophy was introduced. Ospemifene is a selective estrogen receptor modulator, and is well absorbed orally. Once daily therapy with meals is the recommended dosing. Its official indication is for dyspareunia associated with vulvovaginal atrophy, and it meets official criteria for improvements in vaginal pH and moisture.

Vasomotor Symptoms

Systemic estrogen therapy

Hormone therapy in women who have had a hysterectomy is quite straightforward: you need only to have your patient decide whether she wants oral or transdermal therapy.

For the patient with a uterus, multiple decisions are required: (i) oral or transdermal administration; (ii) choice of progestin and (iii) how should she take her progestin therapy. Some women would prefer to have regularly scheduled bleeding, and would do better with a cyclical progestin; some would do anything to avoid resumption or continuation of menses, and would prefer a daily progestin, with possibility of lighter but unscheduled bleeding. It is very important to have these discussions with your patient, as they will determine her compliance with therapy. You also should assure your patient that she can easily switch from one strategy to another, if she really finds one not to her liking.

In 2014, a new product was introduced to the market. Using the knowledge that selective estrogen receptor modulators, or tissue selective estrogen agonist/antagonists, can block estrogen activity on certain receptors, a SERM was introduced to block estrogen stimulation on the endometrium. The SERM, known as bazedoxifene, was marketed with conjugated estrogens, for women with a uterus. This combination is an alternative to continuous combined estrogen and progestin therapy, and is associated with a lower risk of unscheduled bleeding. It avoids issues of systemic progestin therapies.

Oral vs. transdermal estrogens

Oral therapy was the mainstay of estrogen therapy for the first 50 years of its use. Transdermal estrogens were introduced in the 1980's, in the form of patches. Topical gels and sprays were introduced in the first decade of the 21st century.

The principle of transdermal estrogens is simple. By direct absorption into the bloodstream, transdermal estradiol avoids first pass metabolism in the liver. By avoiding the liver, you avoid increases in many clotting factors, triglycerides, and sex hormone binding globulins. Unfortunately, you lose the significant increase in HDL seen with oral estrogen therapy.

However, by avoiding increases in certain proteins, you minimize the increased risk of thromboembolic phenomena noted with oral estrogens, and you may achieve higher levels of free estrogen and testosterone, by minimizing any increase in SHBG. Oral estrogens produce a greater increase in estrone than estradiol, whereas transdermal estrogens lead to a greater estradiol to estrone ratio. Gall bladder disease is somewhat less likely with transdermals.

From a symptom point of view, women with migraines tend to do better with the constant blood levels achieved with patches. Women with a tendency towards nausea usually tolerate any transdermal better than oral administration. Oral estrogen rarely increases blood pressure; transdermal estrogen has an even lesser likelihood of doing so.

Some women have sensitive skin, and cannot tolerate patch therapy. If they wish to try a transdermal, they would do better with a daily gel application. Some do not do well with any topical therapy, and clearly prefer the oral approach.

The decision on patch vs. topical gel is mostly based on personal preference -- although there are some metabolic differences, the most important variable is your patient's happiness and compliance with her method. The blood levels of estrogen achieved with standard doses of gels and sprays are modest; typically, you will see a level of approximately 30-40 picograms per ml with recommended dosing. This level is quite sufficient for osteoporosis prevention. However, it may not be sufficient to relieve vasomotor symptoms. Patches are available in dosages of 0.025 mg up through 0.1 mg; the 0.1 mg level will achieve a level of 90 picograms per ml. Occasionally women will need even higher levels to control hot flashes.

Given the significant safety of both oral and transdermal therapy, I let my patients choose the method they would prefer, barring a significant medical complication. Comfort with a method will lead to better compliance with therapy.

There is no difference between transdermal and oral therapy regarding cancer issues. Transdermal and oral estrogen both increase the risk of endometrial cancer, if administered unopposed to women with a uterus. Both have the same potential of increasing the risk of diagnosing breast cancer with prolonged therapy with continuous combined progestin therapy.

Which estrogen?

All transdermal products contain 17 beta estradiol, which is plant derived. Many different oral estrogens are available. In the United States, the most popular oral estrogen for many years has been Premarin, or conjugated equine estrogens, derived from pregnant mares' urine. A combination of many different estrogens, Premarin was the estrogen used in the Women's Health Initiative. Several oral products of plant based conjugated estrogens are currently available as well.

Although the FDA considers all estrogens under the same class warning, there have been theoretical questions raised in the debate of conjugated estrogens vs. estradiol therapy. Some investigators have discussed the possibility that while estradiol is strictly an estrogen agonist, certain components of conjugated estrogens may have estrogen antagonism activity at the level of the estrogen receptor, possibly accounting for the decreased risk of breast cancer in unopposed conjugated estrogen users.

From a pharmacokinetic perspective, the half life of estradiol is shorter than that of conjugated estrogens; for some women using oral estradiol, twice daily administration is more effective for symptom relief than once daily administration. Switching to a conjugated estrogen may be more practical.

Although I routinely do not measure blood estrogen levels, assessing blood levels of conjugated estrogens is difficult, in that you cannot measure the levels of all components. Measurement of serum estradiol is not helpful in these women. If you really want to measure an estrogen level, you may need to switch these women to a roughly equivalent dose of estradiol, and assess where you are.

How do different estrogens compare in dosing?

You cannot give exact equivalence in estrogenic potency from product to product. We use the following as approximations:

1 mg oral 17 beta estradiol = 0.45-0.625 mg conjugated estrogens = 5 micrograms ethinyl estradiol = 0.05 mg transdermal patch.

Knowledge of these levels is helpful in explaining to patients why you are transitioning them from even a low dose oral contraceptive to hormone therapy, if they are now fully menopausal. Most patients and many health care providers do not realize that even the lowest dose combination oral contraceptive has far more estrogen than menopausal hormone therapy.

What about bioidentical hormone therapy?

In the wake of the WHI, many American women abandoned hormone therapy. Many women were not symptomatic with the cessation of therapy. Many women became symptomatic, and tried alternative therapies, which either did not achieve relief of their hot flashes, night sweats and sleep disorders, or produced unwelcome adverse side effects from their therapy.

Women were thus quite eager to hear of products that would relieve their symptoms, with minimal side effects. They also wanted to believe that these "new products" would have no downside risk, such as any increased risk of the detection of breast cancer, with prolonged therapy.

This set the stage for the emergence of "bioidentical hormones." Proponents told women exactly what they wanted to hear. They told women that if they purchased products from compounding pharmacies, they would have no complications related to their therapies. They had no data to support their contentions, but many willing listeners who were quite symptomatic turned to this therapy.

Some compounding pharmacies do produce high quality products; estradiol is a hormone approved by the FDA for use in the United States. However, regulation of products from the myriad of compounding pharmacies is limited; there can be considerable variation in both purity and amount of active product. Compounding pharmacies also often supply estriol in their products; estriol is not approved by the FDA for usage in the United States, and should not be supplied by any regulated pharmacy.

Many patients confuse the thought of "bioidentical" with "plant derived." All estradiol products in this country use plant sources, namely soybeans or yams. Patients also need to be reminded that just because

a product is plant derived, it does not mean that it is totally safe to use, in an unregulated manner. Digitalis is derived from the foxglove plant; most medical providers have taken care of patients who died or were seriously ill with digitalis toxicity.

Women's health care providers have been prescribing "bioidentical hormones" for decades. 17 beta estradiol is the most active estrogen produced by the ovary. When administered transdermally, it gets into the bloodstream exactly as it would if produced by the ovary. All prescription transdermal estrogens are bioidentical; estradiol is of course also available for oral administration.

Oral micronized progesterone is available in the United States in two forms: a pill, marketed as Prometrium, which has the micronized progesterone dissolved in a peanut oil base; and a vaginal product, known as Prochieve or Crinone. Both of these products are bioidentical -- that is, they are the same as the progesterone manufactured by the ovary. Both of these products are available through regular pharmacies, and are FDA regulated, and have been prescribed for many years. Indeed, when a patient who is already on a transdermal estrogen and micronized progesterone comes in for a visit, requesting bioidentical hormones, you can explain to her that she is already on bioidentical hormones.

Should you measure serum estradiol and FSH levels*?*

I seldom measure estradiol levels. In general, you do not need a blood estradiol level in a woman who is 53 years old, has skipped three menstrual periods, and is having hot flashes, to confirm that she is perimenopausal. A low estradiol level and a high FSH will not tell you if she will never experience another period, nor will it tell you when another menses may occur.

There are certain circumstances when an estradiol level is quite valuable. If you have a 35 year old woman with a similar history, an estradiol and FSH will be quite helpful is assessing the cause of her symptoms. Hyperthyroidism can present with exactly the same symptoms. If this young woman is hoping to start a family, you need to be able to assess her reproductive capacity as soon as you can.

If you have a menopausal woman on hormone therapy, and she is still symptomatic, blood estrogen measurements can be quite helpful to assess adequacy of replacement. Some women will have surprisingly low estradiol levels, despite what you think should be adequate replacement. If her estradiol level is good, then you need to look to other causes of hot flashes, such as hyperthyroidism, other medications, infections such as tuberculosis, or certain malignancies, such as lymphomas.

Non-medically educated proponents of "bioidentical hormones" often recommend to women that they have their "hormone levels" measured premenopausally, so that their health care providers can "match" their levels postmenopausally to these earlier levels. What these advocates do not understand is that in the premenopausal women, estradiol levels vary from 40-400 picograms per ml during one normal menstrual cycle. We also know that post menopausal women typically require very low levels of estrogen to control symptomatology; no one needs a level of 400 picograms per ml to control hot

flashes. Recommendations from all professional societies recommend "the lowest dose of estrogen consistent with treatment goals."

Similarly, most "bioidentical" proponents recommend the use of salivary hormone measurements. The vast majority of scientific literature supports the use of blood levels to accurately assess hormone levels; salivary levels are quite variable.

Continuous vs. cyclical progestin therapy

As estrogen use climbed in the US in the 1960's, we saw a rise in the occurrence of endometrial carcinoma. The addition of progestins to estrogen therapy reduced the incidence to that of the control population. Initially, progestins were dosed in a cyclical manner. Estrogens were given either all month, or skipping the last 5 days of the month; and progestins were given for 10-12 days, mimicking the luteal phase. At the end of the progestin administration, women typically experienced a withdrawal bleed.

But the one thing most women enjoyed about menopause was the absence of periods. So in efforts to induce amenorrhea, a daily regime of estrogen and a smaller dose of progestin was introduced. Women would not cycle, but they often experienced breakthrough bleeding. Women earliest in the menopausal transition seemed to experience the most erratic bleeding. Daily progestin therapy also seemed most efficacious in preventing endometrial hyperplasia.

Concomitantly, studies emerged on breast cancer risks with hormone replacement therapy. The majority of literature through the 1990's did not show a significant increased risk of breast cancer with estrogen alone therapy. However, as combination therapy of estrogen and progestin expanded, studies emerged at the end of the 20th century showing a very slight increased risk of breast cancer with long term estrogen and progestin exposure. Many gynecologists tried to come up with regimes that would maximize endometrial protection, while minimizing progestin exposure for breast concerns.

A range of choices of progestin therapy emerged. In the United States, the most popular progestin was medroxyprogesterone acetate. Europeans favored norethindrone. Combination pills were manufactured combining different oral estrogens with these two compounds. Combination transdermal patches contained estradiol and levonorgestrel or norethindrone.

Are all progestins created equal?

Menopause clinicians have noted for years that many women are relatively progestin intolerant. About 20% of women treated with MPA (Medroxyprogesterone acetate) complain of mood swings, irritability, and breast discomfort. Half of these women will improve with norethindrone therapy; the other half (about 10% of all women) do not tolerate norethindrone, either.

Other options do exist for these women. Half of the 10% will tolerate natural micronized progesterone; some do better when it is administered vaginally. Nonetheless, about 5% of women still are uncomfortable with all choices.

We do have options. Drospirenone, a derivative of 17 alpha spirolactone, was developed for use in oral contraceptives. Its endometrial protective effect makes it effective in menopausal hormone therapy; its anti-aldosterone activity decreases the bloating effect of estrogen. It is available for continuous combined therapy, coupled with estradiol.

The levonorgestrel coated IUD, although created for contraceptive purposes, can be used to provide progestin protection to the endometrium, when a woman is administered systemic estrogen therapy. Although some of the progestin is absorbed systemically, levels are quite low, minimizing progestin exposure. For the woman who is still perimenopausal, it will also provide effective contraception.

The French Epic Study has suggested that unlike synthetic progestins, long term exposure (eight years) to natural micronized progesterone does not increase breast cancer risk. No randomized prospective trials have examined this question. Oral micronized natural progesterone can be associated with drowsiness or dizziness. Most women will do best with it administered at night; even then, some will report sleepiness during the day. Also the formulation Prometrium as manufactured in the United States is made in a peanut oil base; for peanut allergic women, a compounding pharmacy can make up micronized progesterone in a different base.

Many women have had ablation procedures premenopausally. Even if they achieved amenorrhea from the procedure, they still require progestin therapy with estrogen therapy, as some glandular tissue may remain. Similarly, for women who have had supracervical hysterectomies who continue to menstruate post procedure, menopausal HT requires progestin therapy as well.

As mentioned above, for women with a uterus, the SERM bazedoxifene is now available combined with conjugated estrogens. Bazedoxifene is not associated with mood changes. Women on estrogen and bazedoxifene have a very small risk of bleeding.

ALTERNATIVE MEDICAL THERAPY

Many women require more than lifestyle and over the counter remedies for their menopausal symptoms. Some women do have contraindications for hormonal therapy; some prefer non-hormonal options. Several choices are available for these women.

Selective Serotonin (and Norepinephrine) Reuptake Inhibitors

The first use of SSRIs was in the treatment of vasomotor symptoms in men receiving GnRH agonist therapy (Leuprolide) for treatment of advanced prostate cancer. This use rapidly expanded to women

with breast malignancies. Many SSRIs have been used, with reasonable efficacy. When SNRIs became available, they were used as well to treat hot flashes.

Unfortunately, anti-depressants have significant potential side effects. Many women experience weight gain and decreased libido with their use. Both of these complaints are often experienced by menopausal women, and many practitioners are concerned about exacerbating these symptoms with therapies designed to help another symptom. However, if the woman is also experiencing depression, these drugs may have dual activity.

If one chooses to treat menopausal symptoms with SSRIs, one needs to monitor the patient for emergence of side effects. Often a switch to a different drug in this category may be helpful.

In 2013, the first non-hormonal medication for vasomotor symptoms was approved by the FDA. (The use of all other antidepressants for vasomotor symptoms is officially off label.) Brisdelle is 7.5 mg of paroxetine, and is too low a dose for relief of depression; its use is exclusively for relief of vasomotor symptoms. At this low a dose, it has been shown to avoid the side effects of weight gain and lack of libido.

Gabapentin

Gabapentin is widely used in neurology, for indications of seizure control, neuropathic pain, and headaches. Yet another use was described several years ago, when gabapentin was found to be effective for hot flash therapy.

Once again, the limitations of gabapentin are its side effect profile. Many women report somnolence from the medication. Others report significant bloating related to the medication. Starting with a low dose can be helpful, titrating up the dose to alleviate symptoms while trying to minimize adverse side effects.

Other options

Several other medical options have been used over the years. Antihypertensives, both alpha and beta blockers, have been tried. Of course, in the normotensive woman lowering blood pressure is not ideal. Antihypertensives can decrease libido as well. Given the relatively low efficacy of these drugs, they are seldom used today.