MENOPAUSAL HORMONE THERAPY

Dr.Mozhgan.vahabi
Fellowship of Infertility

- INTRODUCTION — Natural menopause is defined as the permanent cessation of menstrual periods, determined retrospectively after a woman has experienced 12 months of amenorrhea without any other obvious pathologic or physiologic cause.
- It occurs at a median age of 51.4 years and is a reflection of complete, or near complete, ovarian follicular depletion, with resulting hypoestrogenemia and high follicle-stimulating hormone (FSH) concentrations .
- The menopausal transition (perimenopause) occurs after the reproductive years, but before menopause, and is characterized by irregular menstrual cycles, endocrine changes, and symptoms such as hot flashes.

- CLINICAL MANIFESTATIONS — It is characterized by irregular menstrual cycles and marked hormonal fluctuations, often accompanied by hot flashes, sleep disturbances, mood symptoms, and vaginal dryness .In addition, changes in lipids and bone loss begin to occur, both of which have implications for long-term health.
- Hot flashes — occur in up to 80 percent of women . However, only approximately 20 to 30 percent of women seek medical attention for treatment

- This results in low serum estradiol concentrations and vasomotor symptoms (hot flashes) in the majority of women. Estrogen is the most effective treatment available for relief of hot flashes and for other menopausal symptoms as well.
- Approximately 50 percent of women eventually develop symptoms of vulvovaginal atrophy, including vaginal dryness and dyspareunia, now collectively termed: genitourinary syndrome of menopause (GSM).

- Menopausal hormone therapy (MHT) is commonly used to treat vasomotor symptoms and genitourinary syndrome of menopause (GSM). The benefits of MHT outweigh the risk for healthy, **symptomatic** women who are **within 10 years of menopause** or younger than age 60 years and who do not have contraindications to MHT *(such as a history of breast cancer, coronary heart disease [CHD], a previous venous thromboembolic event or stroke, or active liver disease).*

- Timing of exposure — Data from a primate model [21], two observational studies in postmenopausal women [22,23], a meta-analysis of clinical trials [24], a coronary angiographic study [25], and secondary analyses from the WHI [18,26] all suggest that the timing of exposure to MHT is an important factor in determining subsequent cardiovascular risk. The use of MHT in the early menopausal years does not appear to be associated with an excess risk of CHD when compared with older postmenopausal women. This has been referred to as the "timing hypothesis."
- The WHI population was an older population (mean age 63 years) when compared with most observational studies; the older age at the time of MHT initiation would be expected to be associated with more subclinical atherosclerosis at baseline, with advanced or complex atherosclerotic lesions that may be more susceptible to the prothrombotic, proinflammatory effects of estrogen. In contrast, starting MHT soon after menopause may not cause harm (or may possibly be beneficial) because advanced, unstable atherosclerotic plaques have not yet formed

- MHT is effective for the treatment of menopausal hot flashes and vaginal atrophy caused by hypoestrogenism.
- However, *it is not recommended for the prevention of chronic disease such as prevention of cardiovascular or bone disease.*

ESTROGEN FORMULATIONS AND ROUTES OF ADMINISTRATION

- ESTROGEN PREPARATIONS — Estrogen is available in many forms: oral, transdermal, topical gels, emulsions and lotions, intravaginal creams and tablets, and vaginal rings. In some countries, estrogen can also be given as a subcutaneous implant
- Estrogen doses used for women who have menopausal symptoms are typically lower than doses used to treat women with primary ovarian insufficiency (POI).

- Women being treated for menopausal symptoms such as hot flashes require systemic estrogen.

- women being treated only for vulvovaginal atrophy (now referred to as "genitourinary syndrome of menopause" [GSM]) should be treated with low-dose vaginal estrogen rather than systemic estrogen.

- — All types of estrogen are effective for relieving hot flashes.
- In a meta-analysis of 24 trials of menopausal estrogen in 3329 postmenopausal women, **the frequency of hot flashes decreased** more in those receiving estrogen (weighted mean difference -18 hot flashes per week compared with placebo; 95% CI -22.86 to -12.99; 75 percent reduction) .
- **The severity of hot flashes also decreased** more with estrogen compared with placebo.

- Systemic estrogens — Systemic estrogen is most often administered orally or transdermally .There are several important differences in the effects of these preparations:
- Estrogens administered orally, but not transdermally, undergo hepatic metabolism, the "first-pass effect." The high portal vein estrogen concentrations seen with oral administration increases the hepatic production of most proteins produced by the liver, including thyroxine-binding globulin (TBG), corticosteroid-binding globulin (CBG), sex hormone-binding globulin (SHBG), triglycerides, high-density lipoprotein (HDL) cholesterol, and clotting factors, whereas their production is only minimally increased by transdermal estrogen administration.

- The concentration of estrogen in the hepatic portal system after oral administration is 4 to 5 times higher than that in the periphery.
- Because of first-pass metabolism in the liver, oral estradiol results in a **circulating estrone to estradiol ratio of approximately = 5. with transdermal administration, the ratio is = 1.**

- Oral estrogen — A number of oral estrogen preparations are available (table 1):
- Oral micronized 17-beta estradiol is structurally identical (bioidentical) to the main product of the premenopausal ovary. Oral 17-beta estradiol is poorly absorbed unless it is micronized, in which case it is absorbed through the lymphatic system. Therefore, all commercially available oral 17-beta estradiol products are micronized.

Some estrogen products

Drug and United States brand name	Available strengths
Estrogen preparations and doses for the management of vasomotor symptoms	
Oral estradiol*	
Estrace ¶	0.5, 1, 2 mg
Oral esterified estrogen*	
Menest	0.3, 0.625, 1.25 mg
Oral CEE*	
Premarin	0.3, 0.45, 0.625, 0.9, 1.25 mg
Oral estrogen-progestin combinations	
Prempro Δ	0.3 mg CEE/1.5 mg medroxyprogesterone, 0.45/1.5 mg, 0.625/2.5 mg, 0.625/5 mg
Prefest	1 mg estradiol/0.09 mg norgestimate (cyclic)
Activella, Amabelz, Mimvey ¶	0.5 mg estradiol/0.1 mg norethindrone acetate, 1 mg/0.5 mg
FemHRT, Jevantique Lo	2.5 mcg ethinyl estradiol/0.5 mg norethindrone acetate
Jinteli	5 mcg ethinyl estradiol/1 mg norethindrone acetate
Angeliq	0.5 mg estradiol/0.25 mg drospirenone, 1 mg/0.5 mg
Oral CEEs and bazedoxifene	
Duavee	0.45 mg CEE/20 mg bazedoxifene

- Conjugated equine estrogens (CEEs) are comprised mostly of estrone sulfate with small amounts of equilin sulfate, dihydroequilin sulfate, and many other estrogens and are derived from pregnant mares' urine. In order for estrogens to appear in the urine, they must undergo conjugation to become more polar and soluble in water.

- Ethinyl estradiol, the estrogen used in almost all oral contraceptive preparations. Ethinyl estradiol is much more potent than the other estrogens used for MHT and, therefore, is used in very low doses (5 mcg). Ethinyl estradiol is used in at least one combined estrogen-progestin product that contains 2.5 to 5 mcg of ethinyl estradiol with 0.5 or 1 mg norethindrone acetate.

- Source — Most oral estrogen preparations, with the exception of CEEs, are derived from plant sources. There is no evidence that plant-derived estrogens have any safety and efficacy advantages over those derived from pregnant mare urine (eg, CEE).

- The potency, and therefore the doses, of these estrogen preparations differ, but they differ little in efficacy . In general, **0.625 mg of conjugated estrogens or esterified estrogen is considered equivalent to 1 mg of micronized 17-beta estradiol, 0.05 mg of transdermal estradiol, or 5 mcg of ethinyl estradiol**

- These doses protect bone and relieve vasomotor symptoms in most women. Lower doses are effective for vasomotor symptoms in many women*; most experts recommend starting with low-dose estrogen unless the patient has severe symptoms.* The dose can be titrated up if symptoms are not completely relieved by the low dose of estrogen.

- We most often start women on either a transdermal or oral preparation.
- **We prefer 17-beta estradiol over other estrogens such as conjugated equine estrogens (CEE) because it is structurally identical (bioidentical) to the main estrogen secreted by the ovary.**

TRANSDERMAL ESTROGEN ADMINISTRATION

- Transdermal estrogen — There are many transdermal estrogen preparations available that contain 17-beta estradiol with a wide range of dosing options, from 14 to 100 mcg/day.
- A transdermal dose of 50 mcg/day is approximately equivalent to 1 mg of oral 17-beta estradiol and a 0.625 mg daily oral dose of conjugated estrogens .
- It can be applied once daily on an arm, anywhere from the wrist to the shoulder, or the thigh, without rubbing or massaging.

- The lowest-dose patch containing 0.014 mg of 17-beta estradiol is approved for prevention of osteoporosis. In some women, that dose is also adequate for relief of hot flashes.
- For women with a uterus, addition of a progestin is recommended, although the optimal interval for its administration is not known. For this low-dose patch (0.014 mg), many clinicians administer a 14-day cycle of oral progestin every 6 to 12 months as suggested by the US Food and Drug Administration (FDA), although this has not been well studied.

SYSTEMIC EFFECTS OF HORMONE THERAPY

- Clotting Factors
- First-pass hepatic metabolism affects the synthesis of clotting proteins, markers of coagulation and fibrinolysis that can influence the risk of thrombosis and CHD events.
- Oral estrogen increases factor VII and prothrombin 1 and 2 fragment, whereas transdermal estrogen decreases factor VII.
- Oral estrogen also increases circulating levels of matrix metalloproteinases, MMP-2 and MMP-9, enzymes that are associated with a tendency for clotting.

- Resistance to APC is an important marker for venous thrombosis in individuals with inherited thrombogenic mutations and even in the absence of these mutations.
- **Oral estrogen increases APC resistance, whereas transdermal estrogen has no significant effect on this marker.**
- Based on this difference, one would predict that transdermal delivery of estrogen would be less likely than oral delivery of estrogen to be associated with VTE.

- The first-pass effect is particularly pronounced with **oral estrogen** formulations and ***raises SHBG levels*** such that total serum estradiol levels are greatly affected.
- A potential advantage of **transdermal treatment** because it has minimal to no effect on SHGB levels is the absence of a reduction in free, unbound testosterone levels (which may have implications for sexual function in a subset of users) as are observed with oral estrogen therapy.

LIPIDS AND HEPATIC ENZYMES

- Both oral and transdermal estrogens reduce total cholesterol, LDL cholesterol, and lipoprotein(a). Compared with transdermal estrogen, **oral estrogen produces significantly greater elevations in HDL cholesterol and increases triglycerides, whereas transdermal estrogen decreases triglyceride levels.**
- Indeed, triglyceride levels markedly elevated in response to oral therapy return to normal when treatment is changed to transdermal administration.
- In addition, oral estrogen therapy is associated with an increased risk of gallstones. This risk is present in current and former estrogen users and is somewhat attenuated with the addition of progestin to estrogen therapy.

INFLAMMATORY MARKERS

- A longitudinal study of 346 postmenopausal women taking oral HT reported that elevated CRP was a strong predictor of future cardiac events, but only in those with increased IL-6 levels.
- It is not certain that the decrease in CRP levels with statins and the increase with oral estrogen are instrumental in clinical outcomes.
- The difference in CRP levels between users of oral versus transdermal therapy, **especially in younger postmenopausal women, is of little clinical significance.**

MYOCARDIAL INFARCTION RISK

- Both oral and transdermal administration of hormone therapy are associated with a decrease in myocardial infarction risk in observational studies.

METABOLIC SYNDROME

- The menopausal transition itself is associated with increased likelihood of metabolic dysfunction.
- However, in a review of several RCTs, it was noted that overall effects on markers of the metabolic syndrome, including **insulin resistance, suggested a neutral or improved metabolic profile.** Despite this favorable effect, in women with the metabolic syndrome, caution is recommended given the increased risk of cardiovascular events.
- **Transdermal estradiol has minimal effects on inflammation, coagulation, and insulin sensitivity.**

EFFECTS IN SMOKERS

- Limited evidence suggests that postmenopausal women who smoke may have a better response to transdermal estrogen than to oral estrogen, including greater reductions in total peripheral resistance, vascular sympathetic tone, and norepinephrine levels, and increased vascular responsivity.

CARBOHYDRATE METABOLISM

- There is little difference between the oral and transdermal methods of delivery on carbohydrate metabolism.
- Both methods have a beneficial impact on central abdominal fat content, glucose levels, and insulin resistance, associated with a reduced risk of developing adult-onset diabetes mellitus.

ORAL VERSUS TRANSDERMAL ADMINISTRATION

- Given that transdermal route is suggested to lessen the risk for thrombotic events, it often is preferred by patients and, when applicable, allows monitoring of serum estradiol levels.

ROLE OF MONITORING BLOOD LEVELS OF ESTRADIOL IN ESTROGEN USERS

- We find measurement of blood estradiol levels very useful in selected patients, such as the patient who requests ever-increasing doses of estrogen for the treatment of symptoms, which in the presence of very high blood levels of estradiol can be confidently diagnosed as psychosomatic.

KEY POINTS

- Sufficient evidence **suggests that transdermal route** of estrogen administration be preferentially considered for the following patients:
- Women deemed at risk for VTE
- Women with spontaneous or estrogen-induce hypertriglyceridemia
- Obese women with metabolic syndrome
- Diabetic and hypertensive women
- Smokers
- hypoactive sexual desire or decreased libido.

VAGINAL ADMINISTRATION OF ESTROGEN

- Very-Low-Dose Method(cream, vagifem , Estring)

- Some patients do not gain full relief from the symptoms of vaginal atrophy with oral or transdermal administration of estrogen. Local vaginal administration makes sense for these patients. Vaginal treatment is especially helpful when a rapid response is desired.
- In addition, there are many women who desire the genitourinary effects of estrogen, but either must or wish to avoid systemic therapy

- Measurement of vaginal pH from the lateral vaginal wall is a simple and inexpensive way to assess adequate treatment of the vagina.
- It has been impressive in our experience and others how an acidic pH (<4.5) obtained from the lateral, outer third of the vagina correlates well with good estrogen effects.

- Estrogen in the form of vaginal creams is absorbed very readily from a vagina with immature, atrophic mucosa.
- Indeed, the initial absorption is rapid, and relatively high circulating levels of estrogen are easily reached.
- As the vaginal mucosa matures, absorption decreases . **This decline takes approximately 3–4 months, after which lesser but still significant absorption takes place.**
- **Effective treatment of vaginalatrophy with minimal absorption can be achieved with the administration of 0.3 mg conjugated estrogens, 2 to 3 times per week.**

- Vagifem is a vaginal formulation that is currently available in the United States as a **tablet that contains 10 µg estradiol (was previously also available in a higher strengthof 25 µg).**
- the initial dose of one tablet daily provides relief from atrophic symptoms within 2 weeks. After the first 2 weeks, the maintenance dose is twice weekly.

- Estring is a 55-mm-diameter silicone ring that contains 2 mg estradiol, with a release rate of 7.5 µg/day for 90 days. European studies have demonstrated that vaginal maturation can be achieved with this ring that can be left in place for 3 months, with a low level of systemic absorption.

- Typically, addition of a progestogen is not indicated with low-dose therapy.
- We believe that treatment with a vaginal cream longer than 12 months requires endometrial surveillance.

- The amount of estradiol delivered in low-dose tablet form or a ring is not sufficient to treat menopausal symptoms, but effectively improves local urogenital atrophy and reduces recurrent urinary tract infections.
- This has been accepted as a method **to relieve atrophic vaginal symptoms in women with contraindications to estrogen treatment**;
- however, systemic effects do occur, although not deleterious effects.

STANDARD DOSE METHOD(VAGINAL)

- A vaginal ring (Femring, estradiol acetate) that releases estradiol acetate provides 50 or 100 µg estradiol per day over a 3-month time.

- The systemic levels achieved effectively suppress hot flushing, and a beneficial impact on bone is to be expected. Endometrial protection requires the addition of a progestin in the presence of a uterus.

Vaginal estrogen preparations for treatment of genitourinary atrophy (inadequate dose to relieve vasomotor symptoms)	
Vaginal ring	
Estring	7.5 mcg estradiol per day, released over 3 months
Vaginal tablet	
Vagifem	10 mcg estradiol per vaginal tablet
Yuvafem	10 mcg estradiol per vaginal tablet
Vaginal cream	
Estrace 0.01%	0.1 mg estradiol per gram cream
Premarin vaginal	0.625 mg CEE per gram cream

PROGESTINS

- — All women with an intact uterus need a progestin to be added to their estrogen to prevent endometrial hyperplasia.
- Women who have undergone hysterectomy should **not receive a progestin, as there are no other health benefits other than prevention of endometrial hyperplasia and carcinoma.**

- We advise taking progesterone at bedtime as some of its metabolites are associated with somnolence. There are reasons to believe that **natural progesterone is safer for the cardiovascular system** (no adverse lipid effects) and possibly the breast.

- Dosing
- — Our first choice of progestin is oral natural micronized progesterone (200 mg/day for 12 days/month [ie, a cyclic regimen that is designed to mimic the normal luteal phase of premenopausal women] or 100 mg daily [continuous regimen]).

- **The most extensively studied formulation for endometrial protection is the synthetic progestin used in the WHI, medroxyprogesterone acetate given in a cyclic (5 to 10 mg/day) or continuous (1.25 to 2.5 mg/day) regimen.** While MPA is endometrial protective, it was associated with an excess risk of coronary heart disease (CHD) and breast cancer when administered with conjugated estrogen in the WHI. In addition, it has unfavorable effects on lipids.
- **In addition, regimens using continuous versus cyclic MPA may be associated with a higher risk of breast cancer.**

- **Frequency**
- — Women taking standard doses of estrogen require monthly progestins.
- Other progestins that have been used include quarterly regimens (progestin administered only every third month).
- **However, quarterly progestin administration is not considered to be adequately protective and cannot be recommended for women taking standard doses of estrogen.**
- **Women taking lower doses of estrogen (eg, 0.014 mg transdermal estradiol), however,** require very little progestin (two 12-day courses every six months).
- Vaginal progesterone inserts are sometimes tried, but endometrial safety data are also limited.

- **Side effects**

- — Common side effects of estrogen include breast soreness, which can often be minimized by using lower doses. Some women experience mood symptoms and bloating with progestin therapy.
- Vaginal bleeding occurs in almost all women receiving cyclic estrogen-progestin regimens and is common in the early months of a continuous estrogen-progestin regimen.

- Some women are unable to tolerate cyclic progestin administration (with any type of oral progestin) because of the mood side effects and bloating.
- For any of these concerns, we suggest switching to a continuous regimen of progestin. This maneuver often resolves the issue of mood symptoms and bloating.

- Two metabolites of progesterone, allopregnanolone and pregnanolone, are believed to be responsible for progesterone's unique sedative effect. **Treatment regimens with micronized progesterone should be taken at bedtime, and these estrogen-progesterone combinations are a good choice for women with sleep difficulties.**

- For women who unable to tolerate either a cyclic or continuous oral progesterone regimen, alternatives include:
- **Vaginal use of micronized progesterone – Vaginal, rather than oral administration of micronized progesterone capsules is easier to tolerate for some women.**
- **Levonorgestrel-releasing IUDs – Some clinicians choose off-label use of the lower-dose levonorgestrel-releasing intrauterine device (IUD.**Lower doses of levonorgestrel-releasing) IUDs for use in menopausal women are available in many countries.

- **Conjugated estrogen/bazedoxifene – Another option is the combination of bazedoxifene, a selective estrogen receptor modulator (SERM), with conjugated estrogen.**
- **This product is available for the treatment of** menopausal vasomotor symptoms and osteoporosis prevention. In this combination, the SERM bazedoxifene prevents estrogen-induced endometrial hyperplasia so that administering a progestin is not necessary.
- Like other SERMs, the risk of VTE is increased with bazedoxifene. No additive effect on VTE has been observed with the CEE/bazedoxifene, but longer studies are needed to fully address this risk.

MENOPAUSAL HORMONE THERAPY: SEQUENTIAL AND CONTINUOUS REGIMENS

- Postmenopausal hormone therapy initially consisted only of sequential regimens that were logical reflections of the cyclic estrogen and progesterone patterns in a premenopausal menstrual cycle.
- Progestin withdrawal bleeding occurs in 80–90% of women on a sequential regimen.
- In the sequential regimen, estrogen is administered daily and progestins for 2 weeks of every month.

- The continuous combined method of treatment evolved to improve patient continuance that was adversely affected by bleeding and other symptoms triggered by the cyclic hormonal changes.
- The addition of a daily dose of a progestin to the daily administration of estrogen allowed the **progestin dose to be smaller, provided effective protection against endometrial hyperplasia, and resulted in amenorrhea within 1 year of treatment in 80–90% of patients.**

- • sequential regimens
- 5 mg medroxyprogesterone acetate
- 1.0 mg norethindrone acetate
- 200 mg micronized progesterone

- • In the daily continuous, combined regimen, progestins are combined with estrogen in the following comparable doses:

- 1.5 or 2.5 mg medroxyprogesterone acetate
- 0.5 or 1.0 mg norethindrone acetate
- 100 mg micronized progesterone

MENOPAUSAL HORMONE THERAPY: ESTROGEN DOSE

- There has been a progressive decrease in estrogen doses in postmenopausal hormone therapy regimens. For many years, the standard dose of estrogen was 0.625 mg conjugated estrogens, 1–2 mg micronized estradiol, 1–2 mg estradiol valerate, or equivalent doses of other estrogens such as 5 μg ethinyl estradiol.
- **Lower doses have been proven on the average to be as effective as these "standard" doses**, providing clinicians and patients with more options. Conjugated estrogens in a dose of 0.3 or 0.4 mg effectively produce a gain in bone density when combined with 1.5 mg medroxyprogesterone acetate, and a dose of 0.5 mg micronized estradiol produces comparable effects.

- *The 0.45/1.5 mg and 0.3/1.5 mg conjugat estrogens/medroxyprogesterone acetate combinations* improve vaginal atrophy, reduce hot flushing, and improve measures of sexual function in a pattern that is quantitatively and qualitatively similar to the 0.625/2.5 mg combination with less mastalgia.
- **These lower-dose combinations are associated with less breakthrough bleeding and a higher rate of cumulative amenorrhea compared with older standard doses and retain the favorable changes in the lipid profile.**
- Vigilance is advised in assessing response with lower doses as there will be more women who respond poorly, probably because of a greater rate of metabolism and clearance.

INFREQUENT PROGESTATIONAL EXPOSURE: LONG SEQUENTIAL REGIMENS

- Experience with extended cycle regimens, however, is very limited. The administration of medroxyprogesterone acetate every 3 months was associated in one study with longer, heavier menses and unscheduled bleeding and a **1.5% incidence of hyperplasia at 1 year,** whereas in another study, overall bleeding was less, but the incidence of hyperplasia was approximately 4%.

- We caution against long regimens in women who may be at an innately higher risk for endometrial hyperplasia and cancer, such as those with a **personal history of endometrial hyperplasia**, those who are **obese**, those who are **insulin-resistant**, and **diabetic women**.

- There are some special conditions that warrant consideration of a **combined estrogen-progestin regimen even in hysterectomized women**:

- In women in whom hysterectomy and bilateral salpingo-oophorectomy is undertaken for management of **endometriosis**, we recommend a combination of estrogen plus progestogen. Cases of adenocarcinoma have been reported in patients with pelvic endometriosis treated with unopposed estrogen.
- Patients who have undergone procedures that have the potential to leave residual endometrium (e.g., a **supracervical hysterectomy**) should be treated with an estrogen-progestin combination
- In women undergoing hysterectomy for management of early stage endometrial **adenocarcinoma**, if HT is being considered for symptom control, a combination regimen is advised given the potential protective action of the progestational agent.
- The combined estrogen-progestin approach makes sense for patients previously treated for **endometrioid tumors of the ovary**.

ROLE OF ANDROGENS IN MENOPAUSE MANAGEMENT

- The total amount of testosterone produced per day, however, is slightly decreased because the primary source, the peripheral conversion of androstenedione, is reduced.
- Because of this decrease, some argue that androgen treatment is indicated in the postmenopausal period.

- The potential benefits of androgen treatment include improvement in psychological well-being and an increase in sexually motivated behavior.
- In a well-designed, placebo-controlled study, lower doses of androgen (but still very pharmacologic, 5 mg methyltestosterone) contributed little to actual sexual behavior, although an increase in sexual fantasies and masturbation could be documented.
- The transdermal testosterone treatment of women improved sexual function compared with a placebo group only in the dose that raised circulating testosterone levels to about 100 ng/dL.

- Any benefit must be balanced by the unwanted effects, in particular, virilization (acne, alopecia, and hirsutism) and a negative impact on the cholesterol-lipoprotein profile.
- It should be remembered that androgens do not protect the endometrium, and the addition of a progestin is still necessary.
- Adding testosterone to an estrogen therapy program has been reported to provide *no additional beneficial impact on the bone or on relief from hot flushes.).*
- ***If testosterone use is considered, our preferred method is to use a product that will allow dose to be titered by measuring the total testosterone blood level with the goal of maintaining concentration in the range of 20–80 ng/dL.***

DEHYDROEPIANDROSTERONE

- Adrenal androgen production decreases dramatically with aging.
- The impressive decline (75–85%) in circulating levels of DHEA that occur with aging (greater in men than in women) has stimulated a search for a beneficial impact of DHEA supplementation.
- The only proven function of DHEA and its sulfate, DHEA-S, is to provide a pool of prohormone for conversion to androgens and ultimately estrogens.
- Systemic DHEA supplementation does not produce improvements in menopausal symptoms, mood, libido, cognition, or memory, but it does increase testosterone and decrease HDL cholesterol.

- In women, 25 or 50 mg/day increased testosterone levels, decreased SHBG levels, and produced adverse effects on the lipid profile
- Presumably, the vaginally administered DHEA is converted locally to estrogen and testosterone within the vaginal tissue. In clinical trials comparing DHEA to 0.3 mg CEE or 10 µg E2 daily, **DHEA was found to be at least as effective as CEE and/or estradiol in improving vulvovaginal symptoms.**
- There was no effect of vaginal DHEA on the following tissues: the endometrium and liver; the effects on the bone are not yet known.

TIBOLONE

- Tibolone, is structurally related to the 19-nortestosterone progestins, a drug that has been widely used in Europe and other countries for many years for hot flashes, is a synthetic steroid whose metabolites have **estrogenic, androgenic, and progestogenic** properties.
- It is not available in the United States. Tibolone reduces vasomotor symptoms when compared with placebo, **but it is less effective than estrogen therapy.**

- It also has a beneficial effect on bone mineral density (BMD), and it may have a modest effect for symptoms of sexual dysfunction. However, tibolone increases the risk of recurrence in women with a personal history of breast cancer, and it may increase the risk of stroke in women over age 60.
- Eating does not affect the metabolism, and tibolone can be taken at any time of the day.

- Tibolone is available in two daily doses, 1.25 and 2.5 mg.

- The vascular, breast, and endometrial effects of tibolone include the following
- Stroke – The Long-term Intervention on Fracture with Tibolone (LIFT) trial, which was designed to determine the effect of tibolone on the risk of vertebral fracture in postmenopausal women (n = 4538, average 68 years), was stopped early because of an excess risk of stroke in women receiving tibolone when compared with placebo .
- However, there were no significant differences in the risk of CHD or VTE between the two groups.

- Mammographic density:
- Tibolone does not appear to increase mammographic density or the frequency of abnormal mammograms requiring follow-up.

- Breast cancer risk – In a meta-analysis of four tibolone trials (a total of 5500 women without a prior history of breast cancer), no excess risk of breast cancer was seen.

- Risk of breast cancer recurrence :
- In women with a personal history of breast cancer, tibolone use does appear to be associated with an increased risk .
- *Based upon these data, tibolone should not be used in women with a history of breast cancer.*

- • Vaginal bleeding/endometrial hyperplasia :

- While some women have vaginal bleeding with tibolone ,the rate of unscheduled bleeding is lower than that for MHT , and many develop amenorrhea.
- In the same trial, tibolone was not associated with an increased risk of endometrial hyperplasia.


THANK
YOU