Cutting Through the Noise

Menopausal Hormone Therapy

In many women 50% of life is now spent in a postmenopausal state…by 2025 more than one billion women globally will be perimenopausal or postmenopausal

Menopause and MHT

- Globally the mean age at natural menopause: 48.8years
- 1966, Feminine Forever, Robert Wilson recommended estrogen as a **'cure' for the 'tragedy of the menopause'.**
- "Opinions about MHT appear to be driven as much by the sociocultural climate as they are by the emerging evidence from clinical trials."

Menopause and MHT in 2024: addressing the key controversies – an International Menopause Society White Paper

Defining Menopause


Menopausal Management

Menopause and MHT

Holistic management

- healthy eating, active lifestyle and preventive immunization (e.g. pneumococcal, shingles),
- screening for chronic disease and cancers,
- avoiding cigarette smoking/excessive alcohol,
- staying social engaged and focusing on wellness.

- Menopause and MHT in 2024: addressing the key controversies – an International Menopause Society White Paper

Evolution of Thought

1990's

Pre-WHI

HRT was right for everyone!

2002-2017

Post- WHI

HRT was terrible for everyone!

Present

HRT is beneficial in appropriate patients.

Hormonal therapy in 2025

WHI and Post-WHI Landscape, 2001-2017

WHI post-intervention data, 2018 - present

Position of ACOG , The Menopause Society (NAMS), The Endocrine Society in 2025

Objectives

Describe 4 criteria for diagnosis of menopause.

Explain overall excess risks vs. benefits of MHT based on age of initiation.

Discuss the concept of personalized medicine to guide MHT counseling

Objectives (con't)

Understand the differences in Bioidentical and Compounded MHT

Articulate indications for and data surrounding Testosterone therapy

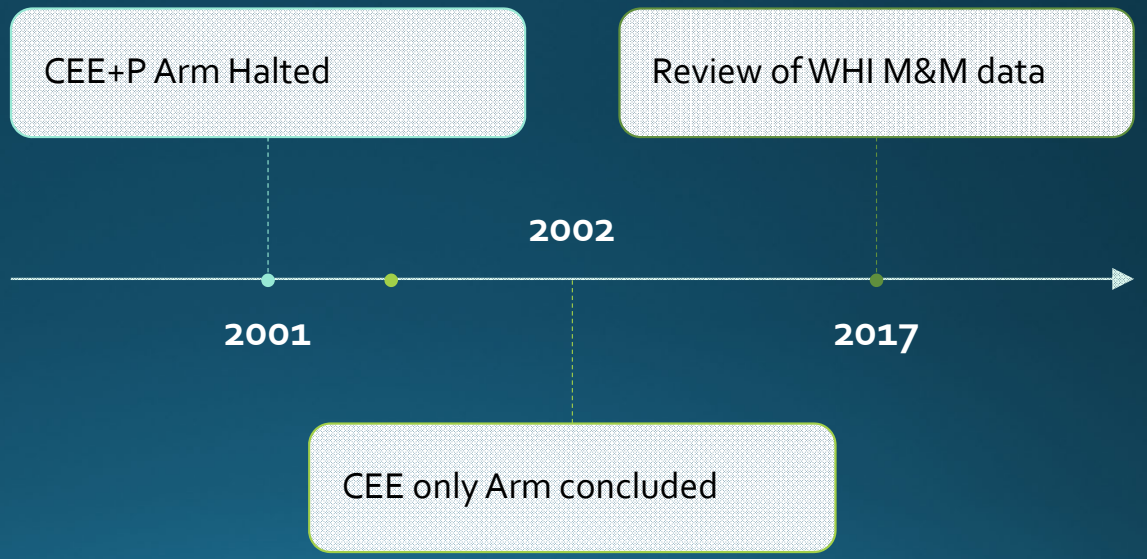
Nomenclature evolution

- Hormone *Replacement* Therapy (HRT) ->
  Hormone Therapy (HT) or
  Menopausal Hormone Therapy (MHT)
- Estrogen replacement therapy -> ET
- Bioidentical: BMHT or BHT
- Compounded: MHT or CHT

Defining Menopause

The Women's Health Initiative

Women's Health Initiative



WHI

- Why?

  To test the observational study conclusions:

  - lower rates of CAD
  - less all cause mortality and dementia

- What?

  - Conjugated Equine Estrogens (CEE) + Medroxyprogesterone Acetate (MPA)

WHI trial details

- 40 centers
- 27,347 women enrolled
  - 16,608 in CEE+ MPA trial
  - 10,739 in CEE only trial
- Randomized Controlled Trial
- Primary Endpoints
  - Cardiovascular deaths
  - Invasive breast cancer

WHI trial details

- Ended early at 5.6 yrs and 7.2 yrs
  - CEE+ MPA trial – inc r/o Breast CA w/o redxn in CV
  - CEE only trial – increased r/o CVA not offset by decreased CV risks
  - Overall absolute increased risks LOW

CEE+MPA arm published

- "Shell shock, Seismic Shift, Sea Change"
- By 2011, 70% decrease in HRT use
  - GOOD: Stopped being used in older women for prevention only
  - BAD: Stopped being used in younger symptomatic women

CEE arm published

- ***Silence***
- No statistical difference in breast cancer risks at study endpoint
- Took longer to see ***decrease*** in breast cancer risks
- Small increase in absolute risks of stroke

Nothing suggested an association of CEE and breast cancer

Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality: The Women's Health Initiative Randomized Trials

Intervention and Extended Post-intervention follow-up

JAMA, 2017 Sep 12;318 (10): 927-938

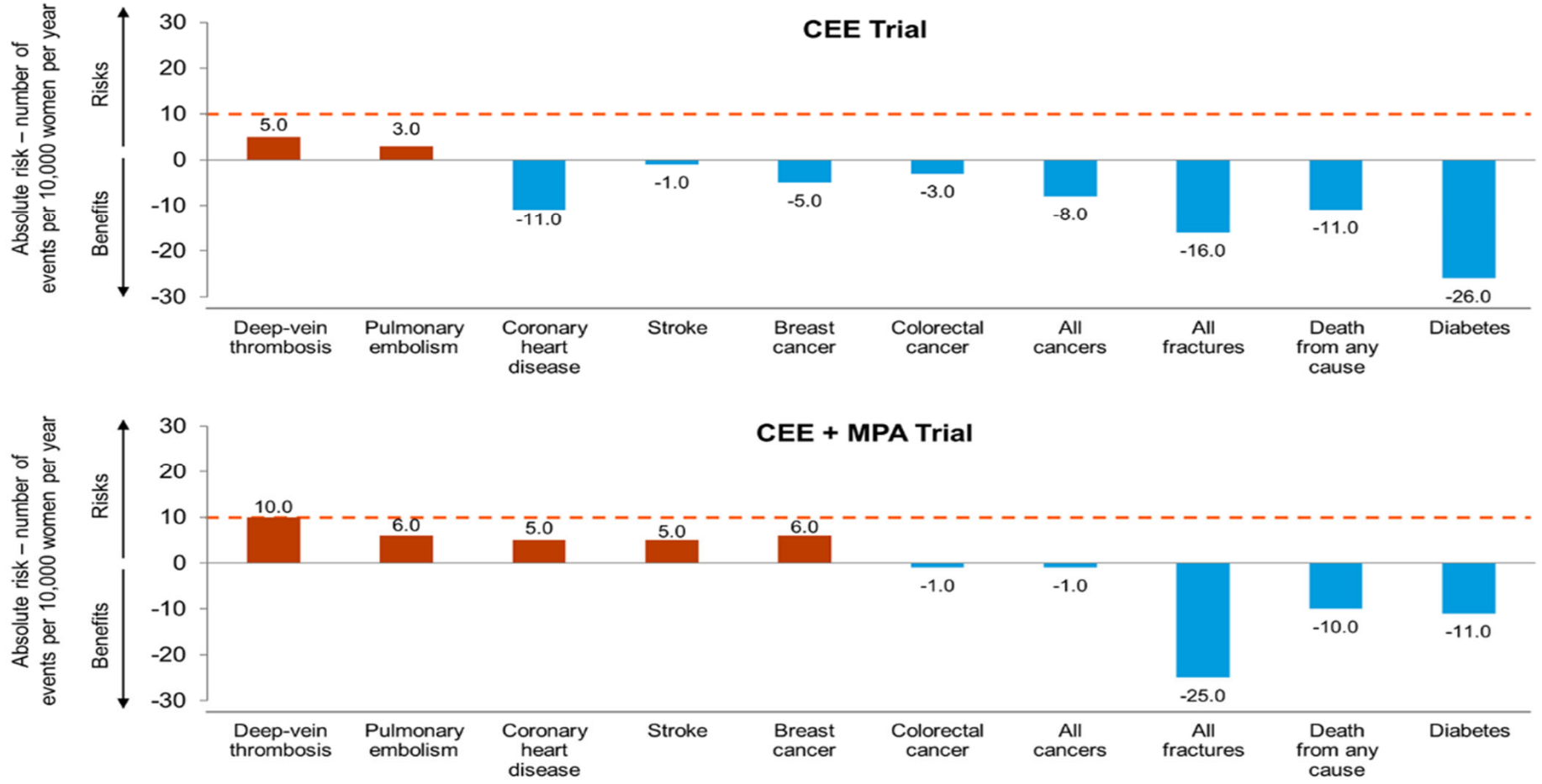


Fig. 1. Benefits and risks of the two hormone therapy formulations, conjugated equine estrogens (CEE) alone or in combination with medroxyprogesterone acetate (CEE + MPA), evaluated in the Women's Health Initiative for women aged 50 to 59 years. Risks and benefits are expressed as the difference in number of events (number in the hormone therapy group minus the number in the placebo group) per 10,000 women per year, with <10 per 10,000 per year representing a rare event (dashed red line). Adapted from Manson JE, et al. *JAMA* 2013;310:1353-1368.

All-Cause Mortality, JAMA 2017

- ***The Bottom Line***

  "Among postmenopausal women, hormone therapy with CEE+MPA for a median of 5.6 yrs or CEE alone for 7.2 yrs was NOT associated with risk of all-cause , cardiovascular , or cancer mortality during a cumulative f/u of 18 yrs"

ACOG

- ***The Bottom Line*, 2020**

  Timing Hypothesis

  "…cardiovascular benefit may be derived when ET or HT is used close to the onset of menopause, but the relationship of duration of therapy to CV outcomes awaits further study."

Safety

- Increased absolute risks EPT and ET are rare (<10/10,000/y) :
  - VTE and gallbladder disease.
- EPT carries a rare increased risk for:
  - stroke and breast cancer
  - If inadequately opposed, endometrial hyperplasia and endometrial cancer.

Safety (cont)

- Absolute *risks are reduced* for:
  - all-cause mortality
  - fracture
  - diabetes mellitus (EPT and ET)
  - and breast cancer (ET) in women aged younger than 60 years

Have we allowed avoidable deaths?

- 4-5 million women not given HRT over last 22 yrs
  - 4500 deaths from Breast CA likely avoided
- Calculated excess deaths in 50-59 yo US women:
  - 18,601 – 91,610 lives

    Cardiovascular deaths

    Cancer deaths

The Mortality Toll of Estrogen Avoidance: an analysis of excess deaths among hysterestomized women aged 50-59 yrs; Am J Public Health. 2013 Sep;103(9):1583-8

ACOG Position Statements

ACOG

- Management of Menopausal Symptoms, Practice Bulletin 141, Jan 2014 (reaffirmed 2018)
- Hormone Therapy and Heart Disease, Committee Opinion # 565, June 2013 (reaffirmed 2020)
- Compounded Bioidentical Menopausal Hormone Therapy, Committee Opinion #532, Aug 2012 (reaffirmed 2023)

ACOG

- Postmenopausal Estrogen Therapy: Route of Administration…, Committee Opinion #556, April 2013 (reaffirmed 2019)
- Treatment of Urogenital Symptoms in Individuals With a History of Estrogen-dependent Breast Cancer, Clinical Consensus #2, Dec 2021

NAMS Position Statement

NAMS Position Statements

- The 2022 hormone therapy position statement of The North American Menopause Society (updating 2012 and 2017 statements) *Menopause*, Vol 29, No. 7, pp. 767-794
- The 2023 nonhormone therapy position statement of the The North American Menopause Society, *Menopause*, Vol 30, No. 6, pp. 573-590
- The Menopause Society Statement on Misinformation Surrounding Hormone Therapy, 2024

The Menopause Society Position

Indicated for:

- Bothersome vasomotor symptoms,
- Genitourinary syndrome of menopause,
- Primary ovarian insufficiency
- Prevention of bone loss and reduction of fracture risk

"Ovarian hormones (estrogen, progesterone, testosterone) do not need to be routinely "replaced" in women undergoing menopause at the average age."

The Menopause Society Statement on Misinformation Surrounding Hormone Therapy, 2024


Cardiovascular
Disease

CAD and All-Cause Mortality

- *2015 Cochrane Review, RCT data w/in 10yrs of Menopause*
  - *Decreased CHD RR 0.52, CI 0.29-0.96*
  - *Decreased all-cause mortality RR 0.7, CI 0.52-0.95*
  - *Increased r/o VTE RR 1.74, CI 1.11-2.73*

Cardiovascular Disease

- WHI Intervention Phase
  - Data combined from both arms: Statistically significant reduction in all cause mortality seen in 50-59 yo women but not older women
- WHI Intervention + Post-intervention
  - Women 50-59 yo: All cause mortality decreased w/ ET or HT use (HR 0.79, CI 0.64-0.96)
  - Younger Women s/p BSO on CEE also with SS decrease ACM
  - (HR 0.68, CI 0.48-0.96)

Cardiovascular Disease

- WHI Coronary Artery Calcium Study:
  - ET adherence for 5 yrs: decrease Coronary calcium OR 0.64
- Progesterone vs synthetic progestins
  - MPA vasoconstrictive, Progesterone vasorelaxative
  - Progesterone has no adverse effects on lipids or BP
  - Progesterone provides endometrial protection – may be used

Cardiovascular Disease and All-Cause Mortality

NAMS

The Bottom Line

Healthy, symptomatic women younger than 60 years or w/in 10 years of menopause onset: Favorable effects of HT on CHD and all-cause mortality should be considered against potential rare increases in risks of breast cancer, VTE, and stroke. (Level I)

ACOG

- ***The Bottom Line*, 2020**

HT and Cardiovascular Disease

- ***Not*** to be used for primary prevention
- Women in good health are at low risk
- Some evidence supports "timing hypothesis"
- Recommends against routine discontinuation at 65


Breast Cancer

Breast Cancer

- The risk related to HT use is low, with estimates indicating a rare occurrence
  - <1 additional case / 1,000 women per year of hormone therapy use
  - 3 additional cases / 1,000 women when used for 5 years with CEE + MPA. (Level I)
- Put the data into perspective: risk similar to that of modifiable risk factors. (Level III)
  - <1 additional case/1000 is slightly greater than risk from 1 glass of wine/day but *less than increase risks from that from 2 glasses/day*

BREAST CANCER *MORTALITY*

- WHI is Only RCT
  - CEE - 20 yrs, *lower* breast cancer mortality – HR 0.60 (CI 0.37-0.97)
  - CEE + MPA – no significant increase – HR 1.35 (CI 0.94-1.95)
- Observational Studies
  - Mortality decreased in most but not all
  - Cancers tend to be be localized, smaller, better differentiated

  Confounded by closer evaluation: Mammograms/CBEs

Breast Cancer (cont)

A preponderance of data does not show an additive effect of underlying breast cancer risk and HRT use on breast cancer incidence. (Level II)

Insufficient data to assess the risk of breast cancer with tissue-selective estrogen complexes (Level II)

Observational evidence: HRT does not further increase risk

- a family history
- after BSO for *BRCA 1* or *2* genetic variants. (Level II)

BREAST CANCER SURVIVORS

- Systemic hormone therapy
  - Generally not advised for survivors of breast cancer
  - HRT use *may be considered* for severe VMS unresponsive to nonhormone options - in conjunction with oncology. (Level III)
- Low-dose vaginal estrogen therapy or DHEA
  - May be considered for genitourinary syndrome - in consultation with oncology.
  - Note increased concern with low-dose vaginal ET for women on aromatase inhibitors. (Level III)


Colorectal Cancer

Colorectal Cancer

- Observational studies suggest a reduced incidence of colorectal cancer in current HT users, with reduced mortality. (Level II)
- In the WHI EPT, but not ET alone, reduced colorectal cancer risk, although cancers diagnosed in EPT users were diagnosed at a more advanced stage.
- WHI - no difference in colorectal cancer mortality with either EPT or ET. (Level I)


Osteoporosis

Bone Density

- **Prevents bone loss** in healthy postmenopausal women
  - with dose-related effects (Level I)
  - Double blinded RCTs
- **Reduces fracture risk** in healthy postmenopausal women. (Level I)
  - WHI
- Discontinuation results in rapid bone loss but no excess in fractures (WHI, Level I)
- FDA **approved for *prevention*** of bone loss, but ***not for treatment*** of osteoporosis. (Level I)

Hormone therapy and Depression

- ET may have antidepressant effects of similar to antidepressant agents in depressed perimenopausal women with or without VMS. (Level II)
- ET is ineffective as a treatment for depressive disorders in postmenopausal women.
- II)

Menopause symptoms
Sexual function

- Systemic HT and vaginal ET:
  - increase lubrication, blood flow, and sensation of vaginal tissues.
- Systemic HT does not improve:
  - sexual function,
  - sexual interest,
  - arousal, or orgasmic response

Routes of Administration
Transdermal vs Oral

- Alleviating VMS: **No** difference
- Presumed benefit of avoiding first pass effects

No trials comparing r/o MI, CVA, Breast CA, VTE

Menopause symptoms
Sexual function

- If sexual function or libido are concerns:

  Transdermal ET may be preferable over oral ET because of minimal effect on SHBG and free testosterone levels.

- Low-dose vaginal ET improves sexual function in postmenopausal women
  with GSM.

- Non-estrogen FDA-approved alternatives for dyspareunia:
  - Ospemifene
  - Intravaginal DHEA.


Vaginal Estrogen

Vaginal Estrogen

- The WHI prospective observational cohort study
  - median follow-up - 7.2 years
  - no increase in cardiovascular disease, pulmonary embolism, venous thrombosis or stroke, or cancer

- The Nurses' Health Study
  - >18 years of follow-up on low-dose vaginal ET
  - No significantly increased risks of breast or endometrial cancer, CVD, total cancer, or all-cause mortality

Vaginal Estrogen

- A comprehensive meta-analysis of prospective observational studies: no association of vaginal ET with breast cancer

  Collaborative Group on Hormonal Factors in Breast Cancer. Lancet 2019;394:1159-1168

- A 2019 meta-analysis of eight studies: no increase in E2 levels after 8 weeks of vaginal ET in women on aromatase inhibitors

  Pavlovic´ RT, et al. The safety of local hormonal treatment for vulvovaginal atrophy in women with estrogen receptor-positive breast cancer … : meta-analysis. Clin Breast Cancer 2019;19:e731-e740.


Testosterone

The Menopause Society Position

Testosterone therapy is Indicated for:

- Hypoactive sexual desire disorder

Testosterone therapy is *Not* Indicated for:

- Treatment or prevention of any age-related condition
- Treatment or prevention of sarcopenia or osteoporosis
- Treatment of mood changes, neurovegetative sx, well being

The Menopause Society Statement on Misinformation Surrounding Hormone Therapy, 2024

Testosterone Therapy

- There is data to support that testosterone may help with:
  - menopausal symptoms
    - FSD and arousal disorders
  - vaginal atrophy
- *There may be adverse, possibly irreversible effects and long-term side effects are unknown.*

Compounded Bioidentical Menopausal Hormone Therapy, ACOG Clinical Consensus, No. 6, 2023

Testosterone Therapy

- Long term effects on CV risk and breast cancer risks are unknown
- Pelleted therapy: potential for better bioavailability but limited data exists to support safety
- Adverse reactions: facial hair, acne, voice change, mood swings, anxiety and AUB

Compounded Bioidentical Menopausal Hormone Therapy, ACOG Clinical Consensus, No. 6, 2023

Testosterone Therapy

"Short-term use of transdermal testosterone can be considered as a treatment option for postmenopausal individuals with sexual interest and arousal disorders who have been appropriately counseled about the potential risks and unknown long-term effects"

Female sexual dysfunction. ACOG Practice Bulletin No. 213, 2019

Testosterone therapy

There is no FDA-approved testosterone formulation for the management of menopausal symptoms. Clinicians and patients should use a shared decision-making framework when considering the use of compounded testosterone for this indication. Based on the lack of safety data and inability to remove the pellet, ACOG recommends preparations other than pellet therapy for the delivery of testosterone.

Compounded Bioidentical Menopausal Hormone Therapy, ACOG Clinical Consensus, No. 6, 2023

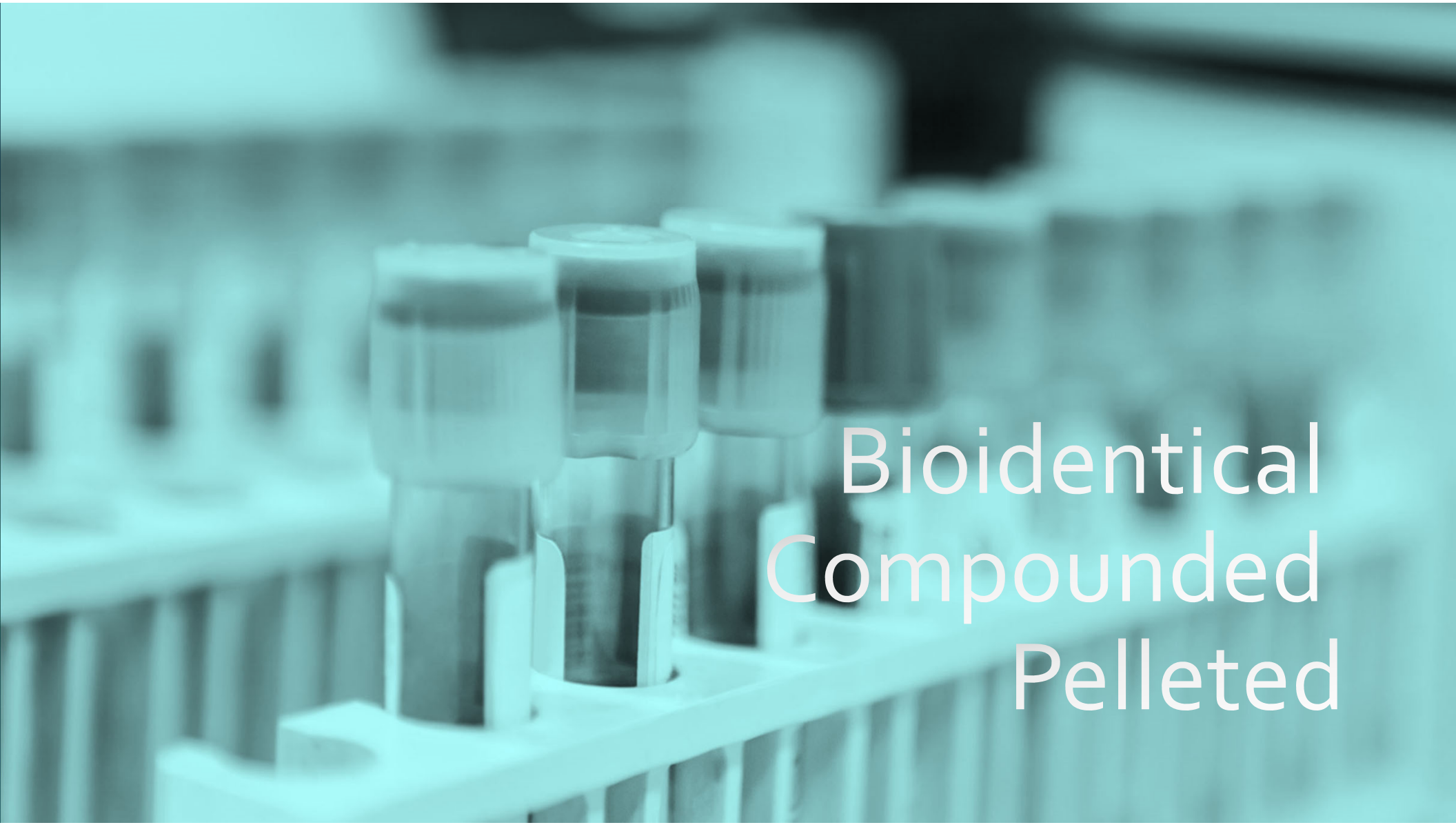

Hormone testing

Hormone testing

- E2 and Progesterone do not meet criteria for testing
- Salivary testing does not offer accurate /precise information
  - Steroid hormones are highly bound and therefore low in saliva
  - Circulating levels do not reflect tissue levels
  - Not FDA approved
- Treat to manage symptoms w/ known safe preparations
- If pt already on Compounded: E2 level 40-100 pg/ml is appropriate
- If pt on pelleted Testosterone: r/o supraphysiologic levels

  20-80 ng/dl appropriate

  Compounded Bioidentical Menopausal Hormone Therapy, ACOG Clinical Consensus, No. 6, 2023


Bioidentical
Compounded
Pelleted

Bioidentical Hormones

- Plant-derived hormones
- Chemically similar or structurally identical to those produced by the body
- Commercially available products approved by the FDA :

  micronized progesterone, estradiol, and dehydroepiandrosterone (DHEA),
- Compounded preparations that are not regulated by the FDA

Compounded Bioidentical Menopausal Hormone Therapy, ACOG Clinical Consensus, No. 6, 2023

Compounded Hormones

- Custom-made for patient according to a clinician's specifications.
- Various routes of administration: oral, sublingual, percutaneous, implants, injectables, and suppositories
- Not standardized dosage
- *Compounded Bioidentical Menopausal Hormone Therapy, ACOG Clinical Consensus, No. 6, 2023*

	FDA-approved HRT	Compounded BHT
Molecular structure	Similar or identical* to human	Identical to human
FDA oversight	Yes	No
Dosage	Monitored: accurate & consistent	No monitored
Purity	Monitored; pure	Not monitored
Safety	Tested; risks known	Not FDA tested; unknown
Efficacy	Tested and proven	Not FDA tested; unproven
Scientific Evidence	Existent; conclusive	Insufficient

Comparison of FDA-approved HT w/ cBHT

FDA Center for Drug Evaluation and Research. Report: Limited FDA Survey of Compounded Drug Products. January 2003.

Counseling about Compounding

- Compounding pharmacies are not required to:
  - report adverse events to the FDA
  - provide the labeling, with data on safety and effectiveness, or warnings.

This may lead to the belief of patient that these drugs are safer.

Compounded Bioidentical Menopausal Hormone Therapy, ACOG Clinical Consensus, No. 6, 2023

Counseling about Compounding

- FDA-approved hormones are recommended
- There is limited safety and efficacy data re:
  - compounded and pelleted MHT
  - Dosing proportions may not result in same safety as FDA studied MHT
- Dosing/purity/absorption/potency may vary

Compounded Bioidentical Menopausal Hormone Therapy, ACOG Clinical Consensus, No. 6, 2023

COMPOUNDED BIOIDENTICAL HORMONE THERAPY

- "The Endocrine Society is concerned that patients are receiving potentially misleading or false information about the bene ts and risks of cBHT. Therefore, the Society supports FDA regulation and oversight of all hormones regardless of chemical structure or method of manufacture."

The Endocrine Society, Position Statement on Compounded Bioidentical Hormone Therapy, Reissued October 2, 2019.


Pellets

“HORMONE OPTIMIZATION **WITH BIOTE”**

- “BIOIDENTICAL HORMONE REPLACEMENT THERAPY **FOR WOMEN**
- Many female patients have reported the benefits of bioidentical hormone replacement therapy for women (female BHRT). Our Method of female BHRT has helped thousands of women reclaim their lives.*
- **FIND A PROVIDER**
- **What Is Female BHRT?**
- *These statements have not been evaluated by the Food and Drug Administration. These products are not intended to diagnose, treat, cure, or prevent any disease.

Safety of HRT vs pBHT

- 539 postmenopausal women
  - pHT 384
  - HRT 155
- Side effects
  - HRT 14.8% vs pBHT 57.6% (P<0.00001, OR 8)
    - PMB HRT15.2% vs pBHT 55.3% (P < 0.0001, OR 7.9)
- Serum levels
  - E2 mean and peak higher in pBHT: HRT 93.4 vs 235 pg/ml
  - Testosterone peak higher: HRT 15.9 vs 194 ng/dL

Safely assessment of compounded non-FDA-approved hormonal therapy vs FDA-approved HT in treating PM women, Xuezhi Jiang, Menopause 2021.

. 2005 Apr 20;97(8):595-602
. 2005 Apr 20;97(8):595-602

Plasma hormone levels and Breast Cancer

Nurses Health Study Cohort

- Prospective, Nested, Case-control
- 1989-1990 with 10 yr f/u
- All using HT at time of blood collection
- 446 women developed cancer, matched to 459 women w/o cancer
- Highest versus lowest quartiles of free and total E2, Testosterone, and SHBG

. 2005 Apr 20;97(8):595-602
. 2005 Apr 20;97(8):595-602

Plasma hormone levels and Breast Cancer

Highest versus lowest quartiles

- Free estradiol (RR = 1.7, 95% CI = 1.1 to 2.7; P(trend) = .06),
- Free testosterone (RR = 1.6, 95% CI = 1.1 to 2.4; P(trend) = .03),
- Women older than 60 years
  - E2 (RR = 2.8, 95% CI = 1.5 to 5.0; P(trend) = .002
  - Free E2 (RR = 2.6, 95% CI = 1.4 to 4.7; P(trend) = .001)

Tworoger S, et al, Plasma Sex Hormone concentrations and Subsequent Risk of Breast Cancer… Journal of the National Cancer Institute, Volume 97, Issue 8, 20 April 2005, Pages 595–602


Conclusions

The Menopause Society

- < 4% of women 50-59 are using MHT
- Not all menopausal women will require / use hormone therapy
- First-line therapy for management of bothersome vasomotor symptoms
- Benefits > risks for most healthy women if
  - initiated younger than age 60 years or
  - within 10 years of menopause onset with appropriate counseling

The Menopause Society Position

Menopausal hormone therapy *Not* Indicated for:

- Primary Prevention of CVD or dementia
- Musculoskeletal conditions other than osteoporosis prevention
- Prevention of Aging
- Management of other primarily age-related changes

The Menopause Society Statement on Misinformation Surrounding Hormone Therapy, 2024

The Menopause Society Position

- "The risks and benefits of hormone therapy need to be individualized and discussed with pa[?]ents in a balanced way, without minimizing risks."
- Systemic MHT should not be used in Breast cancer survivors w/o consultation with their oncologist

The Menopause Society Statement on Misinformation Surrounding Hormone Therapy, 2024

NAMS Position Statement

- ***The Bottom Line***
  - Women less than 60 yo and w/in 10 yrs of menopause :
    - Benefit risk ratio is favorable for use of HRT for VMS and bone loss prevention
  - Women older than 60 yo or greater than 10 yrs from menopause:
    - Benefit risk ratio is less favorable due to increase absolute r/o
      CADz, Stroke, DVT and Dementia

Conclusions

- HT is the most effective treatment for VMS and the genitourinary syndrome of menopause
- HT prevents bone loss and fracture.
- Risks of hormone therapy differ for women depending on:
  - type, dose, duration of use
  - route of administration, timing of initiation, +/- progestogen
- Treatment should be individualized with periodic reevaluation.

Conclusions

- For women ≤60 years or within 10 years of menopause onset and without contraindications, the benefit-risk ratio appears favorable for treatment of bothersome VMS and for the prevention of bone loss and reduction of fracture.
- Based on the WHI RCTs, longer duration *may be more favorable for estrogen therapy* than for estrogen-progestogen therapy.

Conclusions (cont)

- For women who initiate HT **≥10 years** from menopause onset or **≥60 years** or older:

  the benefit-risk ratio appears less favorable than for younger women because of greater absolute risks of coronary heart disease, stroke, venous thromboembolism, and dementia.

ACOG

- ***The Bottom Line, 2018***

Treating Symptomatic Women

- HT is the most effective treatment. (Level I)
- Lowest effective dose of HT for shortest period of time.
- SRI, SNRIs, Gabapentin, & Clonidine are effective alternatives.
- Duration of therapy should be individualize (Level III)

ACOG

- ***The Bottom Line, 2018***
  - **No data to support:**
    - Testosterone, progesterone only or bioidentical compounded HT
    - Phytoestrogens, herbal combinations, or lifestyle modifications
  - **2019** – short term use of transdermal testosterone with appropriate counseling acceptable

ACOG

- ***The Bottom Line, 2019***

  Route of Delivery and VTE

  - CVD, obesity, fracture, renal disease, immobilization or thrombotic disorders increase risk
  - Take into account possible thrombosis-sparing effects of **transdermal estrogens**
    - The Estrogen and Thromboembolism Risk Study

      OR for VTE in oral vs TD: 4.2 to 0.9

NAMS Position Statement

- Advisory Panel of clinicians and researchers considered expert in women's health
- Update to 2017 Position statement
  - Evaluating new literature
  - Assessing evidence
  - Grading strength of evidence for recommendations

NAMS Position Statement

- **Frequency of Adverse Reaction:**

• Very common	≥ 1/10 women
• Common	≥ 1/100 but < 1/10
• Uncommon	≥1/1,000 but <1/100
• Rare	≥1/10,000 but < 1/1,000
• Very Rare	<1/10,000 women

ACOG

- ***The Bottom Line, 2018***

  Compounded Hormones

  - Purity, potency and quality are of concern.
  - Over/Underdosage possible due to differences in bioavailability and bioactivity.
  - No e/o superiority.
  - Coventional HT is *preferred*.

Discontinuation of Hormone Therapy

- Long-term use of hormone therapy, including for women aged older than 60 years, may be considered in healthy women at low risk of cardiovascular disease and breast cancer with persistent vasomotor symptoms or at elevated risk of fracture for whom other therapies are not appropriate. (Level III)
- Hormone therapy

Breast Cancer Incidence
HRT vs ERT

- **CEE + MPA**
  - During: 9 additional cases /10,000 person-yrs therapy (*Rare*)
  - Post-intervention f/u: 20 yrs, HR: 1.28
- **CEE alone**
  - During trial: 7 *less* cases/10,000 person -yrs therapy (NS)
  - Post-intervention f/u: 20 yrs, HR 0.78 (*Statistically significant*)

No RCTs address longer use of HRT or ERT

- observational data suggests increasing risks over time for both

Breast Cancer

- The effect of HRT on breast cancer risk may depend on the type, duration, regimen, prior exposure, and individual characteristics. (Level II)
- Different hormone therapy regimens may be associated with increased breast density (CEE+MPA), which may obscure mammographic interpretation. (Level II)

Breast Cancer

Regular breast cancer surveillance is advised for all postmenopausal women per current breast cancer screening guidelines, including those who use hormone therapy. (Level I)

Bone Density

- ET decreases bone resorption
- In pts w/ osteoporosis RCTs have not shown decrease fractures with HRT
- WHI: BMD significantly increased 4.5% /3.7%
  Fractures decreased by 12/10,000
- Only protective while on ET/HRT
  - 1-2 yrs - BMD at pretreatment levels

HT and Bone Health

- **Prevents bone loss** in healthy postmenopausal women
  with dose-related effects (Level I)
  - Double blinded RCTs
- **Reduces fracture risk** in healthy postmenopausal women. (Level I)
  - WHI
- Discontinuation results in rapid bone loss but no excess in fractures (WHI, Level I)
- FDA approved for *prevention* of bone loss, but *not for treatment* of osteoporosis. (Level I)

Hormone therapy and Osteoporosis
(cont)

- To *prevent bone loss* in the absence of contraindications:
  - For symptomatic women < 60 yrs or within 10 years of onset

    systemic HRT is an appropriate therapy. (Level I)
  - For women with premature menopause without fragility fracture or osteoporosis

    are best served with HRT *or OCPs* rather than other bone-specific treatments, until the average age of menopause, when treatment may be reassessed. (Level II)

Hormone therapy and Osteoporosis
(cont)

- Decisions regarding initiation and discontinuation of hormone therapy should be made primarily on the basis of extraskeletal benefits (ie, reduction of vasomotor symptoms) and risks. (Level III)

CAD and All-Cause Mortality

- 2020 Systematic Review and Meta-analysis of RCTs
  Null effect on ACM, CVA or VTE when initiated w/in 10yrs or before 60yo
- 2019 Systematic Review and Meta-regression analysis of RCTs looking at timing hypothesis
  - Lower OR of CHD, ACM and cardiac mortality (0.61-0.72)
  - Increased OR of CVA, TIA or systemic embolism (1.40)
  - Attenuated when open label trials removed

Cardiovascular Disease and All-Cause Mortality

- Not FDA-approved for primary or secondary cardioprotection. (Level I)
- Personal and familial risk of CHD, stroke, VTE, and breast cancer should be considered when initiating HT. (Level III)
- The effects of HT on CHD may vary depending on when HT is initiated in relation to a woman's age and/or time since menopause onset. (Level I)

Cardiovascular Disease and All-Cause Mortality

- Initiation of hormone therapy in recently postmenopausal women reduced or had no effect on subclinical atherosclerosis progression and coronary artery calcification in randomized, controlled trials.

  (Level I)

Cardiovascular Disease and All-Cause Mortality

- Observational data and meta-analyses:
  - Reduced risk of CHD in women who initiate HT ≤ 60 years and/or within 10 years of menopause.
- Meta-analyses show a null effect of hormone therapy on CHD after excluding open-label trials. (Level II)
- Initiation or HRT > 60 yo or more than 10 or 20 years from menopause onset are at higher absolute risks of CHD, VTE, and stroke…(Level I)


Everything Else

Weight and body composition

- The menopause transition is associated with an increase in body fat and a decrease in lean body mass, which results in an increase in the fat-to-lean ratio and decreased basal metabolic rate.
- Although HT may help attenuate abdominal adipose accumulation and weight gain associated with the menopause transition, the effect is small. (Level II)

Metabolic syndrome and diabetes

- HT significantly reduces the diagnosis of new-onset type 2 diabetes mellitus (DM), but not FDA- approved for this indication. (Level I)
- HT is not contraindicated in otherwise healthy women with preexisting type 2 DM and may be beneficial in terms of glycemic control when used for menopause symptom management. (Level II)

Hormone therapy and cognition

- Not recommended at any age to prevent or treat a decline in cognitive function or dementia. (Level I)
- Initiating CEE+MPA at ≥65 years increased the r/o dementia, with an additional 23 cases per 10,000 person-years . WHI Memory Study. (Level I)

Hormone therapy and cognition

- The effect may be modified by baseline cognitive function (Level II)

- ET may have cognitive benefits when initiated immediately after Hyst/BSO, but HT in the early natural menopause has neutral effects. (Level II)

Hormone therapy and Depression

- possible window of opportunity for the effective use of ET for the management of depressive disorders during the perimenopause. (Level II)
- There is evidence that ET enhances mood and improves well-being in nondepressed perimenopausal women. (Level II)

Hormone therapy and Depression (cont)

- Transdermal E2 + progesterone may prevent the onset of depressive symptoms in euthymic perimenopausal women.
- Data not sufficient to recommend estrogen-based therapies for depression prevention in peri- or postmenopausal pts(Level II)
- Estrogen-based therapies may augment clinical response to antidepressants in midlife and older women. (Level III)

Hormone therapy and Depression
Caveats

- Most studies examined the effects of *unopposed estrogen.*
- Data on estrogen-progestogen therapy /different progestogens are sparse and inconclusive. (Level II)
- Estrogen is not FDA approved to treat mood disturbance. (Level I)

Ovarian Cancer

- **OCP use** -> significant reduction in ovarian cancer risk. (Level I)
- **Current / Recent use of HT** is associated with increased risk of ovarian cancer in **observational** studies (not seen in CEE+MPA in WHI). (Level II)
  - Serous type
  - 1 add'l death/1700-3500 HRT users
  - ET or combined HRT
  - Dissipates w/in 5 yrs

Ovarian Cancer Survivors

- HT does not effect recurrence or survival

  Benefits outweigh risks especially for POI or severe VMS
- Not advised for prior Granulosa Cell Tumors or Serous tumors
- Short-term HT use appears safe in women with BRCA1 and BRCA2 s/p BSO before the average age of menopause. (Level II)

Duration of Use

- Factors that should be considered:
  - severity of symptoms
  - effectiveness of alternative interventions
  - underlying risk for osteoporosis, coronary heart disease, cerebrovascular accident, venous thromboembolism, and breast cancer. (Level III)
- Does not need to be routinely discontinued at 65

Duration of Use

- Longer durations/extended use >65:
  - Periodic reevaluation of comorbidities
  - Consideration of periodic trials of lowering/discontinuing HT. (Level III)
- In the absence of contraindications:
  - *a woman should determine her preferred hormone therapy formulation, dose, and duration* of use, with ongoing assessment and shared decision-making with her provider (Level III)

Menopause and MHT

- Symptoms:
  - Vasomotor symptoms
  - Genitourinary symptoms
- A recent systematic review and meta analysis of prevalence data globally found that joint and muscular discomfort were the most prevalent menopause related symptoms at 65.43%
- We must strive for balance to not "medicalize menopause," while also not trivializing symptoms.

- Menopause and MHT in 2024: addressing the key controversies – an International Menopause Society White Paper


Vaginal Estrogen

Vaginal Estrogen

- The WHI prospective observational cohort study
  - median follow-up - 7.2 years
  - no increase in cardiovascular disease, pulmonary embolism, venous thrombosis or stroke, or cancer

- The Nurses' Health Study
  - >18 years of follow-up on low-dose vaginal ET
  - No significantly increased risks of breast or endometrial cancer, CVD, total cancer, or all-cause mortality

Vaginal Estrogen

- A comprehensive meta-analysis of prospective observational studies: no association of vaginal ET with breast cancer

  Collaborative Group on Hormonal Factors in Breast Cancer. Lancet 2019;394:1159-1168

- A 2019 meta-analysis of eight studies: no increase in E2 levels after 8 weeks of vaginal ET in women on aromatase inhibitors

  Pavlovic´ RT, et al. The safety of local hormonal treatment for vulvovaginal atrophy in women with estrogen receptor-positive breast cancer … : meta-analysis. Clin Breast Cancer 2019;19:e731-e740.

Discontinuation of Hormone Therapy

- Long-term use of hormone therapy, including for women aged older than 60 years, may be considered in healthy women at low risk of cardiovascular disease and breast cancer with persistent vasomotor symptoms or at elevated risk of fracture for whom other therapies are not appropriate. (Level III)
- Hormone therapy does not need to be routinely discontinued in women aged older than 60 or 65 years. (Level III)

RECOMMENDATIONS

When recommendations are provided, they are graded according to these categories:

- Level I: Based on good and consistent scientific evidence.
- Level II: Based on limited or inconsistent scientific evidence.
- Level III: Based primarily on consensus and expert opinion.

Initiation After Age 60 Years

- The safety profile of hormone therapy is most favorable when initiated in healthy women aged younger than 60 years or within 10 years of menopause onset, so initiation of hormone therapy by menopausal women aged older than 60 years requires careful consideration of individual benefits and risks. (Level I)
- Mitigation of risk through use of the lowest effective dose and potentially with a nonoral route of administration becomes increasingly important as women age and with longer duration of therapy. (Level III)
- For women with the genitourinary syndrome of menopause, low-dose vaginal estrogen therapy may be considered for use at any age and for extended duration, if needed. (Level III)