WOMEN'S HEALTH 2020:
Beyond the Annual Visit

Postmenopausal Hormone Therapy

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omnia EDUCATION

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Financial Disclosure

- **Grants/Research:** Agile Pharmaceutical, Evofem, Merck, Sebela Pharmaceutical
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- **Consultant/Advisory Board:** Agile Pharmaceutical, AMAG, American Regent, Bayer HealthCare, Merck, TherapeuticsMD

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Learning Objectives

At the conclusion of this presentation, participants will be able to:

- Discuss with women the endocrinologic changes that occur during perimenopause and menopause
- Identify differences seen across ethnic groups, both physiologically and culturally
- Describe the etiology of perimenopausal and menopausal symptomatology and health impact
- Outline therapeutic options to manage the manifestations of menopause

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When Can IT Start?

A 43-year-old healthy woman presents with monthly menses complaining of 2 months of what she now knows are hot flashes. She is confused. She thought hot flashes came with menopause.

- Does she need any tests?
- What is her diagnosis?
- What therapies can you offer her?

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Any 3 Define Onset of Perimenopause

- New heavy or longer flow
- Shorter menstrual cycle lengths (<25 days)
- New breast tenderness or fibrocystic changes
- New or increased dysmenorrhea
- New mid-sleep awakening
- Onset of night sweats, especially around menses
- New or increased migraine headaches
- New or increased premenstrual mood swings
- Weight gain w/o changes in exercise/food intake

Prior JC, et al. *BC Med J*. 2005;47:534-538.

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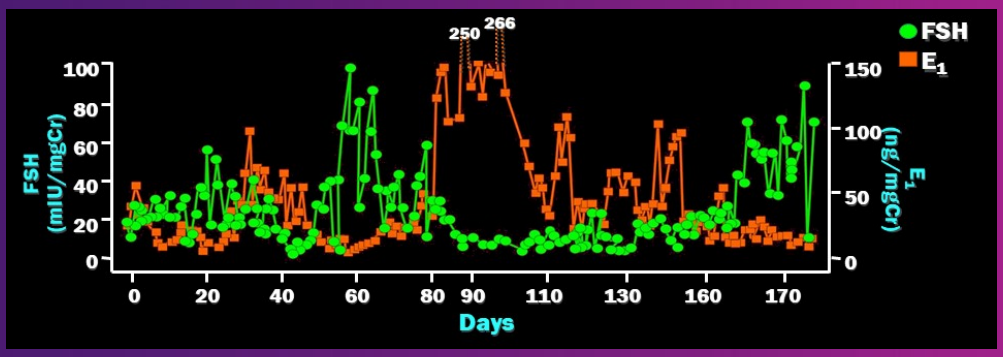
FSH and E_1 Variability in a Perimenopausal Woman



- FSH variability makes diagnosing menopause using a single FSH value unreliable
- Estrogen variability may account for perimenopausal menstrual irregularities

Santoro N, et al. *J Clin Endocrinol Metab*.1996;81(4):1495-1501.
Prior JC. *Endocr Rev*. 1998;19(4):397-428.

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Menopause = Estrogen Deficiency State

- Multiple organ impact:
  - Skin
  - Skeletal
  - Genito-urinary
  - Cardiovascular
  - Central nervous system

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Diagnosing Menopause

- Surgical menopause can be diagnosed after bilateral oophorectomy
- Natural menopause:
  - After 12 consecutive months of amenorrhea with no other etiology
    - Trend toward diagnosis after 6 months of amenorrhea
  - No single biochemical test is a reliable guide before 6 to 12 months of amenorrhea
  - Elevated FSH (>30 mIU/mL) alone not diagnostic
  - One measurement of E1 not diagnostic
  - FSH and E2 levels are not reliable predictors of menopause
    - Variable in perimenopausal women

Sarri G, et al. *BMJ*. 2015;351:h5746.

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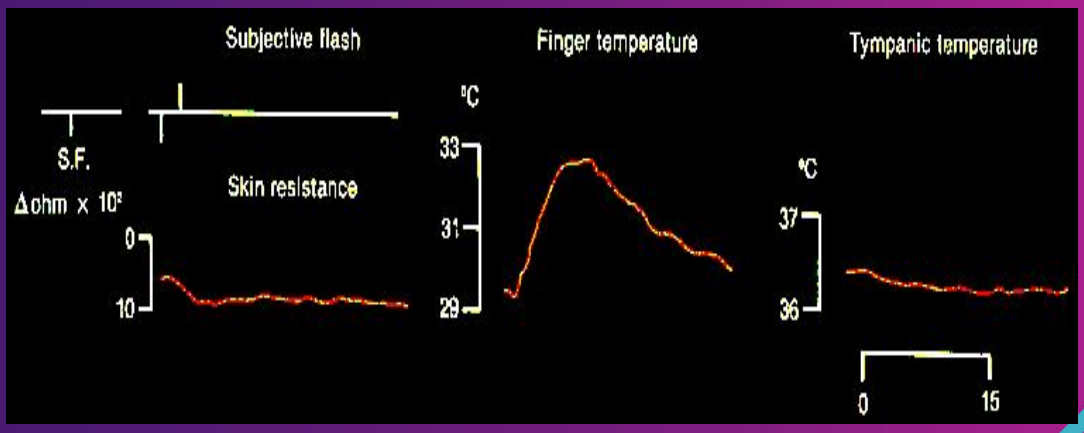
Recorded Changes in Finger and Core Temperatures and Skin Resistance During a Hot Flash Episode in a Postmenopausal Patient



Tataryn IV, et al. *Obstet Gynecol*. 1981;57(3):340-344.

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Different Hot Flash-Related Thermoregulatory Thresholds

	Symptomatic Women	Asymptomatic Women	P Value
T_c sweat threshold (°C)	36.88 ± 0.06	37.42 ± 0.06	0.001
Basal rectal (°C)	36.82 ± 0.09	37.12 ± 0.07	0.023
Maximum sweat rate (mg/cm^2/min)	0.200 ± 0.015	0.128 ± 0.020	0.0001

No difference in BMI, E_2, P_4 or skin fold thickness

Freedman RR, et al. *Menopause*. 2005;12(2):156-159.

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Impact of Ethnicity SWAN

	More Likely To:
African American	Report heavy bleeding Have hysterectomy Have high BMI Report high rates of hot flashes
Hispanic: Puerto Rico Central America	Develop metabolic syndrome, Type 2 DM, anxiety, depression, vasomotor symptoms
Non-Hispanic Caucasian	Low bone density

Santoro N, et al. *Obstet Gynecol Clin North Am*. 2011;38(3):417-423.

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Other Factors Influencing Outcomes

Economic Status	Depressive symptoms, menopausal symptoms, early menopause
High BMI: Perimenopause	Worse vasomotor symptoms, lower gonadotropin and E_2 levels, metabolic syndrome, CVD risk and mood symptoms
High BMI: Postmenopause	No increase in hot flashes ? Reduction in VMS[2]
Obesity related to	Higher androgens, low SHBG, surgical menopause
Timing	Late perimenopause most symptomatic

1. Santoro N, et al. *Obstet Gynecol Clin North Am*. 2011;38(3):417-423.
2. Anderson DJ, et al. *Am J Obstet Gynecol*. 2020;222(5):478.e1-478.e17.

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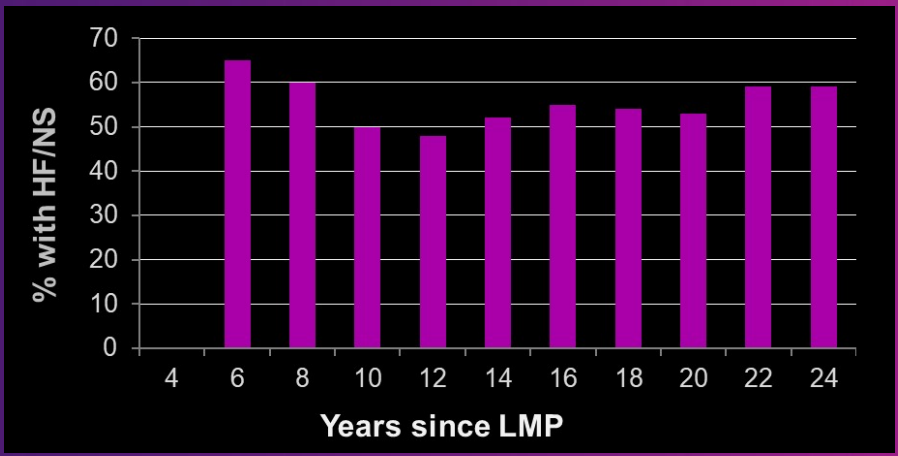
Prevalence, Frequency, and Intensity of Hot Flashes in Older Postmenopausal Women



Hunter MS, et al. *BJOG*. 2012;119(1):40-50.

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VMS and Age-related Health Risks

- Severe VMS and night sweats associated with indicators for age-related risks
  - Cardiovascular disease ↑ 70%[1]
  - Osteoporosis
- VMS associated with greater epigenetic aging[2]
- Factors: racial/minority status, lower education, and greater BMI[1]

1. Zhu D, et al. *Am J Obstet Gynecol*. 2020; online ahead of print.
2. Thurston RC, et al. *J Clin Endocrinol Metab*. 2020;105(4):1221-1227.

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Dosing Ranges for *Nonhormonal* Drugs

Drug	Brand name	Range (mg/day)	Comment
Paroxetine salt	Brisdelle	7.5 mg	Single dose, no titration needed
Paroxetine	Paxil	10-25	Start with 10 mg/d
Citalopram	Celexa	10-20	Start with 10 mg/d
Escitalopram	Lexapro	10-20	Start with 10 mg/d (for sensitive or older women, start 5 mg/d
Desvenlafaxine	Pristiq	100-150	Start with 25-50 mg/d and titrate up by that amount each day
Venlafaxine	Effexor	37.5-150	Start with 37.5 mg/d
Gabapentin	Neurontin	900-2,400	300mg at night, then add 300 mg at night, then a separate dose of 300 mg in the morning
Pregabalin	Lyrica	150-300	

North American Menopause Society. *Menopause*. 2015;22(11):1155-1174.

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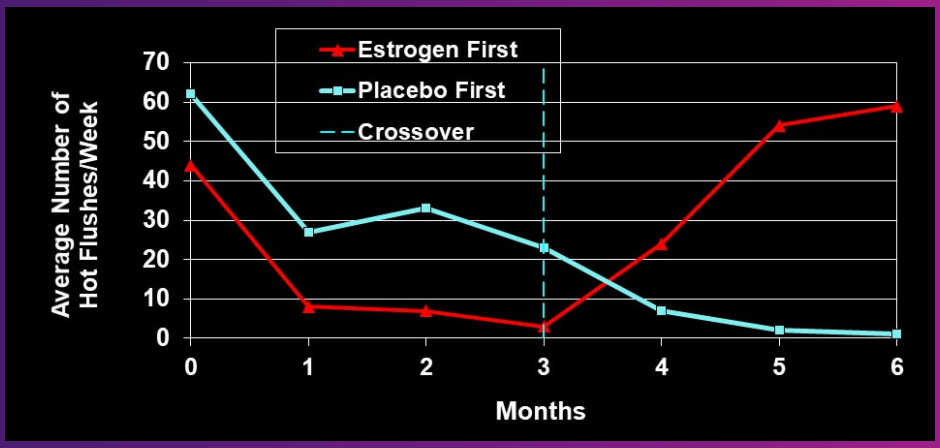
Hot Flash Count During 6-month Trial of Oral Conjugated Equine Estrogen and Placebo



Coope J, et al. *Br Med J*. 1975;4(5989):139-143.

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NAMs Hormone Therapy Dosages

- "The appropriate, often lowest, effective dose of systemic ET consistent with treatment goals that provides benefits and minimizes risks for the individual woman should be the therapeutic goal. The formulation, dose, and route for HT should be determined individually and reassessed periodically"
- Importance
  - Replaces "lowest dose for shortest time" with greater latitude in prescribing

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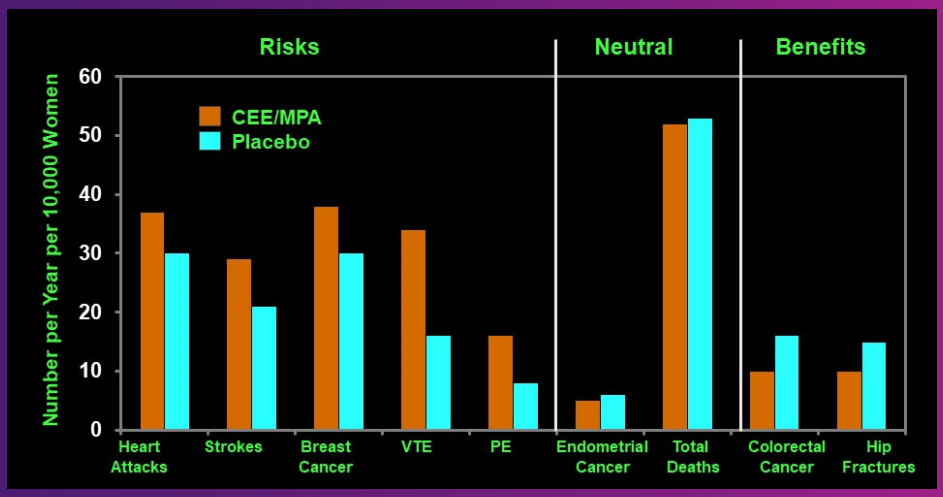
WHI CEE/MPA Results: Number of Cases/Year in 10,000 Women



Adapted from Women's Health Initiative Participant Website. June 2002 HRT Update.

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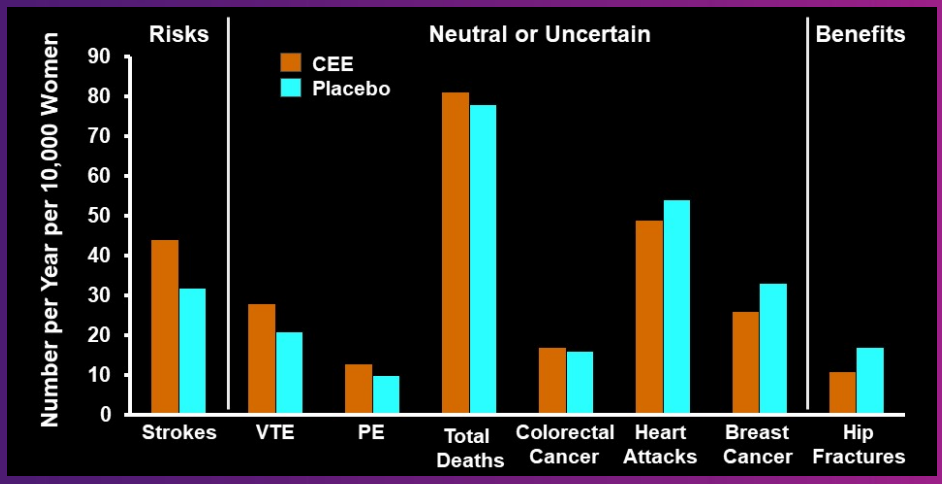
WHI CEE Alone Results: Number of Cases/Year in 10,000 Women



Women's Health Initiative Steering Committee. *JAMA*. 2004;291(14):1701-1712.
Posted at WHI Participants Website. WHI Hormone Program Update, 2004.

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WHI: Lessons Learned 2020

- Neither EPT nor ET prevented coronary heart disease in total WHI population[1]
- Subgroup analyses
  - Women <60 and <10 years from LMP with HT (EPT)
    - No increase in CHD risk[1]
  - Women <60 and <10 years from LMP with ET only[2]
    - 32% reduction in all-cause mortality over long-term follow-up if BSO done before menopause
  - Women with ovaries on ET – no impact

1. Manson JE, et al. *Menopause*. 2020;27(8):918-928.
2. Manson JE, et al. *Ann Intern Med*. 2019;171(6):406-414.

20

Postmenopause Hormone Therapy and Type 2 Diabetes

- Meta-analysis of 107 trials estimated the risk of developing type 2 diabetes was reduced by 30% in nondiabetic postmenopausal women taking postmenopausal hormone therapy[1]
- WHI suggested timing hypothesis
  - T2D lower in younger women; higher in older women[2]
  - Decreases 10/1000 younger women treated for 5 years
- Impact of estrogen action on insulin-stimulated glucose disposal rate varies by time since LMP[3]
  - Benefit ≤6 years
  - Harm ≥10 years

1. Salpeter SR, et al. *Diabetes Obes Metab*. 2006;8(5):538-554.
2. Margolis KL, et al. *Diabetologia*. 2004;47(7):1175-1187.
3. Pereira RI, et al. *J Clin Endocrinol Metab*. 2015;100(12):4456-4462.

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NAMS: VTE Risk with MHT

- WHI entire cohort analysis VTE in women <60 years
  - HT RR 1.74 (95% CI, 1.1-2.73)
  - VTE risk emerges in first 1-2 years
    - Decreases in time
  - Women with BMI>30 – baseline risk 3-fold higher
  - With HT – risk doubles again
- Limited observational studies suggest lower VTE risk with transdermal estrogen
- Lower doses of oral ET may lower risk
- Micronized progesterone may be less thrombogenic
- No excess VTE risk with vaginal estrogen

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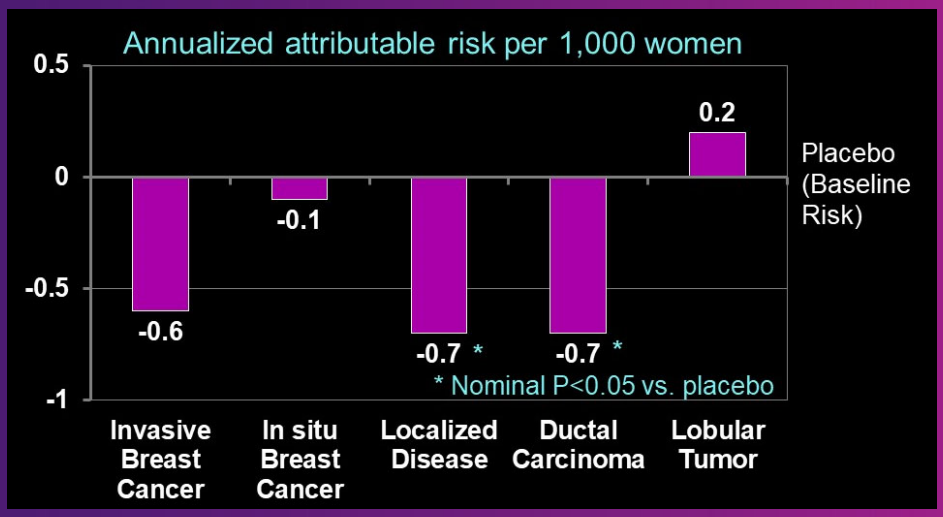
WHI E-Alone Substudy Attributable Risk for Breast Cancer



Stefanick ML, et al. *JAMA*. 2006;295(14):1647-1657.

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Menopausal Hormone Therapy: 20 Years Later Breast Cancer Incidence and Mortality

- 20-year follow-up of 27,347 postmenopausal women in WHI
  - Mortality information available for >98%
- CEE alone associated with lower breast cancer incidence
  - HR = 0.78 (95% CI, 0.65-0.93)
- CEE alone associated with lower breast cancer mortality
  - HR = 0.60 (95% CI, 0.37-0.97)

Chlebowski RT, et al. *JAMA*. 2020;324(4):369-380.

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Menopausal Hormone Therapy: 20 Years Later Breast Cancer Incidence and Mortality

- CEE + MPA associated with higher breast cancer incidence
  - HR = 1.28 (95% CI, 1.13-1.45)
- CEE + MPA associated with no increase in breast cancer mortality
  - HR = 1.35 (95% CI, 0.94-1.95)

Chlebowski RT, et al. *JAMA*. 2020;324(4):369-380.

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Vasomotor Symptoms: Gels

- Estradiol gel in 3 doses
  - 1 mg/day, 0.5 mg/day, 0.25 mg/day*
- Hot flash reductions at 12 weeks:
  - 70%, 79%, 86.6% (placebo 38.9%)
- Once daily on skin of upper thigh (5”x7”)
  - Alternate sides every other day
  - Allow to dry before dressing
  - Don’t wash site for 1 hour
  - Sunscreen and other lotions may change systemic exposure
- Brand name: Divigel

*Delayed impact (week 7)

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Tissue Selective Estrogen Complex (TSEC)

- SERM: Bazedoxifene 20 mg
- Estrogen: conjugated estrogens
  - 0.45 mg, 0.625 mg
- Reduces hot flash frequency and intensity
- Prevents bone loss
- No uterine or breast stimulation
- Improvements in HRQoL, sleep, treatment satisfaction
- Brand name: Duavee

Mirkins S, et al. *Maturitas*. 2014;77(1):24-31.
Archer DF, et al. *J Womens Health (Larchmt)*. 2016;25(11):1102-1111.

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Nonpharmacologic Therapies: NAMS

- Lifestyle adaptation: reconsidered
  - Layered clothing
  - Paced respiration
- Other
  - Cognitive behavioral therapy
    - Does not reduce frequency of hot flashes
    - Helps women cope with symptoms
  - Hypnotherapy
    - 74% vs. 17% fewer hot flashes
    - 80% vs. 15% reduced severity scores
  - Other potential options
    - Weight loss, stellate ganglion block
    - Mindfulness-based stress reduction, S-equol soy

Jacob JA. *JAMA*. 2016;315(1):14-16.

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Gabapentin and Pregabalin Systematic Review with VMS

- Structural analogs of neurotransmitter GABA
  - Reduction of adrenergic hyper-reaction
  - Widening of thermoregulatory zone in hypothalamus
- Most common dose of gabapentin was 900 mg
  - Maximum dose 2400 mg
- Hot flash frequency composite severity scope was reduced by (- 1.62)
- Results similar to fluoxetine and venlafaxine
  - Estrogen better

Shan D, et al. *Am J Obstet Gynecol*. 2020;222(6):564-579.e12.

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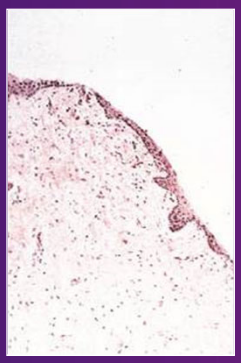
Nonhormonal Treatments for GSM

- Vaginal moisturizers
  - Hydrate vaginal mucosa and lower vaginal pH
- Vaginal lubricants to remove friction
  - Water, silicone, mineral oil, or plant-based
- Topical anesthetics
  - Topical lidocaine
- Pelvic floor therapy
- Microablative and nonablative laser therapies
- Counseling (especially for cancer survivors)

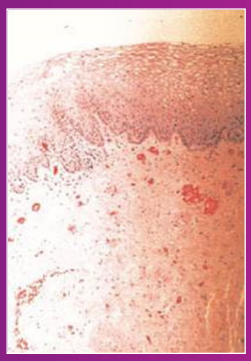
Crean-Tate KK, et al. *Am J Obstet Gynecol*. 2020;222(2):103-113.

30

Effects of ET on Vaginal Epithelium



6 weeks of estrogen



Without Estrogen - Atrophic

With Estrogen[1]

- High concentration of estrogen receptors[2,3]
- Most efficient response with local application[3,4]

1. Freedman M (unpublished data).
2. Bachmann GA, et al. In: Lobo RA, ed. *Treatment of the Postmenopausal Woman: Basic and Clinical Aspects*. 2nd ed. Lippincott Williams & Wilkins; 1999:195-201.
3. Elia G, et al. *Obstet Gynecol Surv*. 1993;48(7):509-517.
4. Weinberger MW. *Clin Obstet Gynecol*. 1995;38(1):175-88.

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Non-Estrogen Hormonal Options for GSM

- Vaginal DHEA (Prasterone)
  - Intracrinology: absorption into cell, conversion to estrogen, then inactivation
  - Increases thickness, collagen fiber compactness, and mucification of epithelium
  - Little systemic impact
- Selective estrogen receptor modulators (ospemifene)
  - Antiestrogenic impact on breast
  - Endometrial safety in 12-month study
  - Contraindications in US same as estrogen

Crean-Tate KK, et al. *Am J Obstet Gynecol*. 2020;222(2):103-113.

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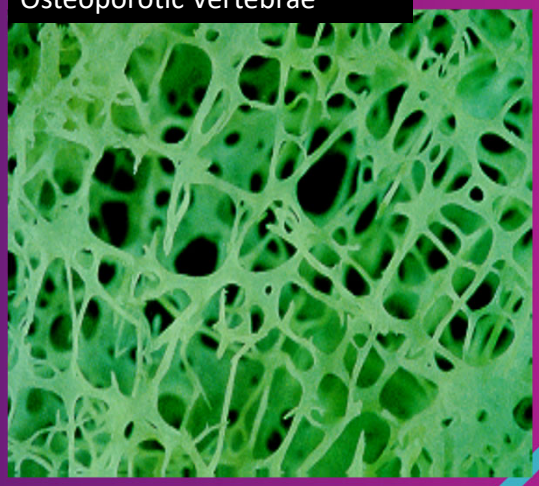
Epidemiology of Osteoporosis

Normal Vertebrae

Osteoporotic Vertebrae



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Osteoporosis Treatments

- Lifestyle measures:
  - Stop smoking
  - Stop/slow alcohol intake
  - Adequate calcium and vitamin D*
  - Regular exercise
  - Prevent falls
- Medications that stop bone loss (slow osteoclasts)
  - Hormonal therapy, other antiresorptive agents
- Medications that increase bone formation (stimulate osteoblasts)

*No reduction in fracture[1]

1. Tai V, et al. *BMJ*. 2015;351:h4183.

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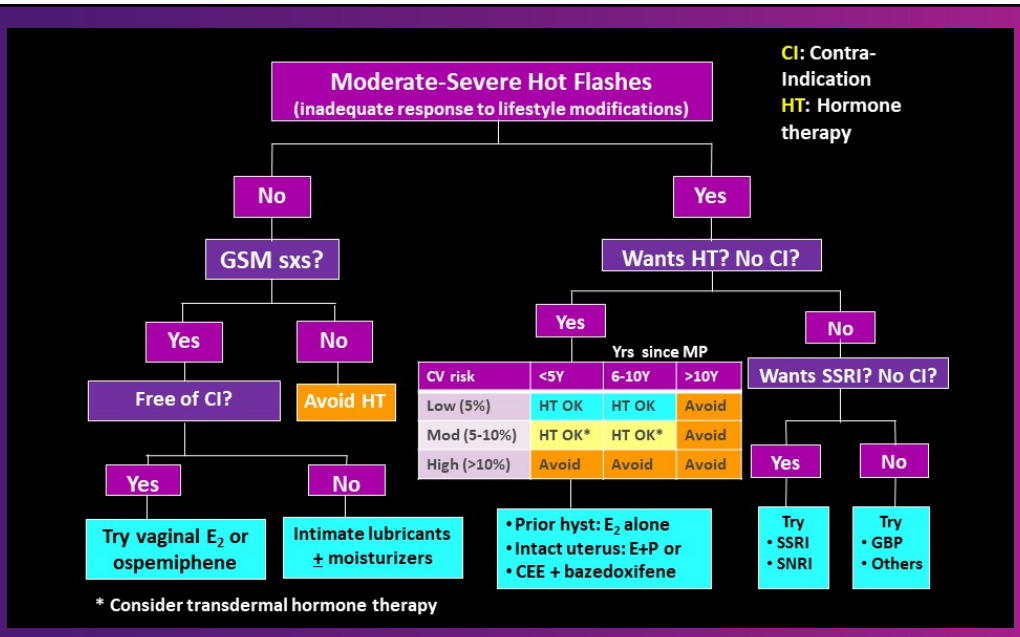

Manson JE, et al. *Menopause*. 2015;22(3):247-253.

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Compounded Bioidentical Hormones An Endocrine Society Scientific Statement

The widespread availability of FDA-approved bioidentical hormones produced in monitored facilities demonstrates a high quality of safety and efficacy in trials; therefore, there is no rationale for the routine prescribing of unregulated, untested, and potentially harmful custom-compounded bioidentical HTs.

Clinicians are encouraged to prescribe FDA-approved hormone products according to labeling indications and to avoid custom-compounded hormones.

Santoro N, et al. *J Clin Endocrinol Metab*. 2016;101(4):1318-1343.

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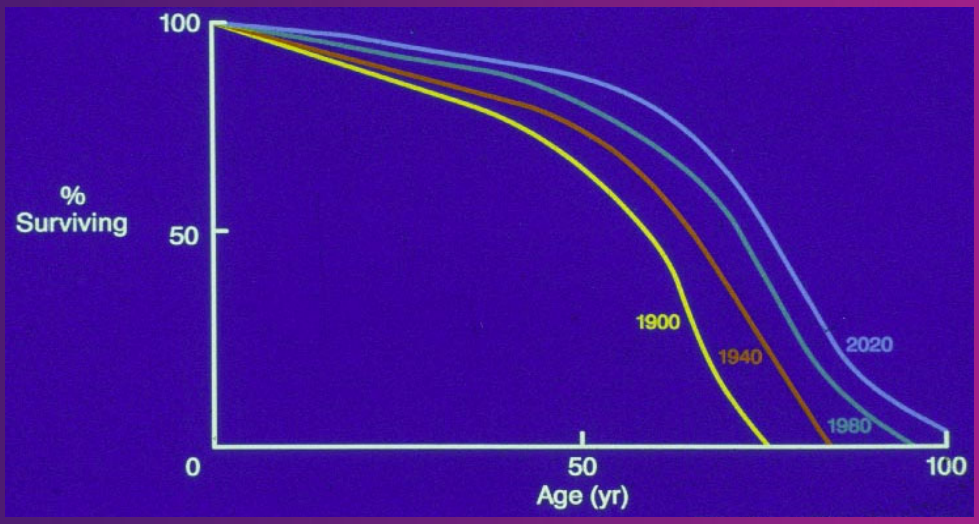
Common Misconception About Change in Life Expectancy



Fries JF, Crapo LM. *Vitality and Aging*. 1981.

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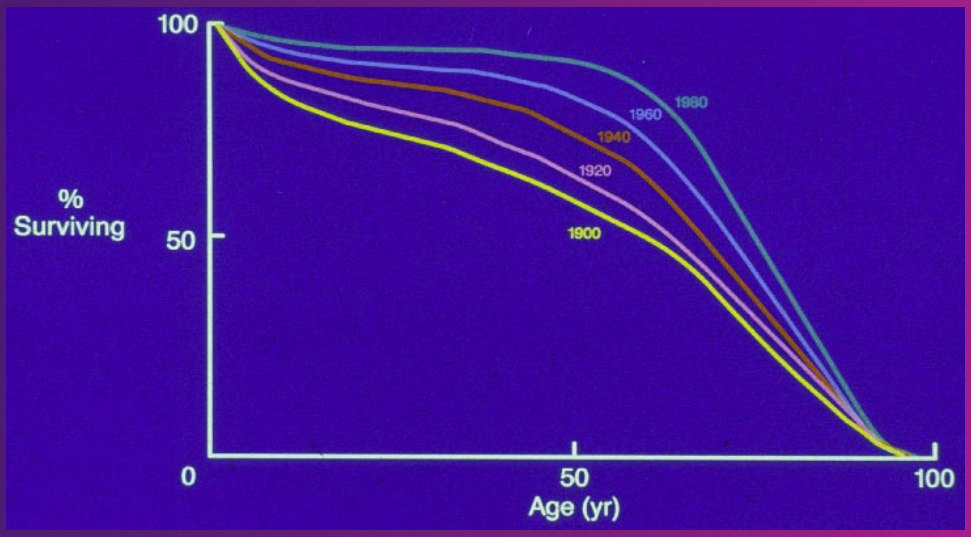
Human Survival Curves: US, 1900-1980



Fries JF, Crapo LM. *Vitality and Aging*. 1981.

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The Rectangular Survival Curve