Menopause Hormone Rx: Where Are We Now?

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Disclosure

I have no financial interests or relationships to disclose.

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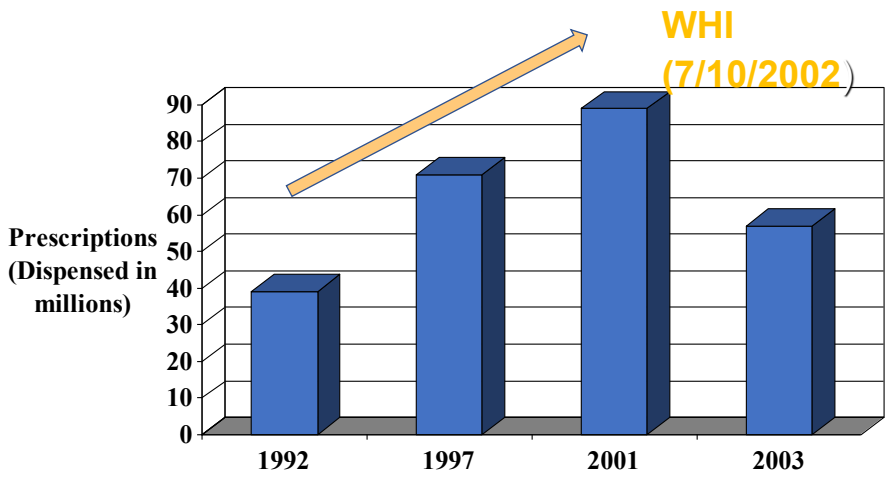
Estrogen Use in the United States



JAMA 2004;291(1):47-53

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MHT: Reasons for Increase in Use

- "greying of America"
  - estimated 58 million American women over age 50 years
  - average life span: 79 years
- delay or prevention of osteoporosis, ? CHD, Alzheimer's, colon cancer, diabetes

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Women's Health Initiative
Los Angeles Times- July 10, 2002

LUIS SINCO / Los Angeles Times

...e leads protesters, irate over police ...an Jackson, at Inglewood City Hall.

Risks of Hormone Therapy Stop Study

Medicine: Large clinical trial finds more cases of breast cancer and cardiovascular disease after long-term use of post-menopause drugs.

By ROSIE MESTEL
TIMES STAFF WRITER

Three years ahead of schedule, scientists have unexpectedly halted a critical clinical trial testing the effects of hormone replacement therapy on women after menopause because of a slight but significant increase in the risk of breast cancer, heart attacks, blood clots and strokes.

The trial, which tracked 16,608 women taking either the hormones estrogen and progestin or a placebo for five years, was brought to an end after a review in late May made it clear that the risks of the hormone regimen outweighed the benefits.

The findings are to be published in the Journal of the American Medical Assn. next week but were released Tuesday because of their medical importance.

The study, part of a large government-funded research program known as the Women's Health Initiative, deals a serious blow to the long-term use of hormone replace-

said Dr. Howard Judd, chairman of obstetrics and gynecology at Olive View-UCLA Medical Center and a principal investigator at one of the three study sites in the Los Angeles area. "The results should have profound effects on hormone replacement—or if they don't, they should."

Many women may still opt to take hormones for short spells to treat symptoms of menopause such as hot flashes, night sweats, mood swings and vaginal dryness.

The researchers also found in their study that hormone replacement therapy led to reductions in risks for colorectal cancer and hip fractures.

Such benefits, however, can be achieved with other drugs and lifestyle changes that do not confer the same risks as hormone replacement therapy, the researchers said.

"You're hard pressed to say 'take estrogen to prevent colorectal cancer' if you see someone's more likely to develop breast cancer, have a heart attack, a stroke or a clot in the lungs or the legs," said Marcia Stefanick, associate professor of medicine at Stanford University, principal investigator of one of the 40 clinical centers and chairwoman of the Women's Health Initiative steering committee.

The authors concluded there is no longer any rationale for taking hormones for long-term protection

Please see HORMONES, A11

...port Offers ...Beating

a copy of which was shared with The Times on Tuesday. "He didn't respond and continued to stare at me."

But a family member said Donovan Jackson suffers from a speech impediment and a hearing disability that prevents him from responding promptly.

"You tell him something, and he doesn't get it right then," said his cousin Talibah Shakir, a sixth-grade teacher in Los Angeles. "He's slow to react."

ROD STEIGER: 1925-2002

Method Actor Infused His Roles With Raw Intensity

By LORENZA MUÑOZ
and SUSAN KING
TIMES STAFF WRITERS

Rod Steiger, an Oscar-winning actor whose chameleon-like ability to inhabit diverse characters placed him firmly among a generation of ac-

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Women's Health Initiative - Initial Findings

Estrogen + Progestin Arm

ADVERSE EVENT	CEE + MPA *	PLACEBO	HAZARD RATIO
CORONARY HEART DISEASE	37	30	1.29 (95% CI 1.02-1.63)
BREAST CANCER	38	30	1.26 (95% CI 1.00-1.59)
DVT/PULMONARY EMBOLUS	34	16	2.11 (95% CI 1.58=2.82)
STROKE	29	21	1.41 (95% CI 1.07-1.85)

*** 0.625 mg CEE AND 5 mg MPA**

JAMA 2002;288:321

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Angeles Times

Thursday, June 21, 2007 : Valley Edition

Doctors change course again on estrogen therapy

Indicating a 2002 report was a false alarm, new research says hormones are safe if taken shortly after menopause.

By Thomas H. Maugh II
Times Staff Writer

Nearly five years after government scientists told women that estrogen replacement therapy increased their risks of heart attack and stroke, researchers have largely reversed their position, concluding that the drugs are beneficial for many after all.

Continuing analysis of the original data indicates that the researchers raised a false alarm for most women and that, if women begin taking the hormones shortly after menopause, the drugs do not raise the risk of heart disease and might even lower it.

The latest findings, published in today's New England Journal of Medicine, show that taking estrogen for seven years or more after menopause reduces calcification of the arteries — a key indicator of atherosclerosis — by as much as 60%. High levels of calcification are generally considered a predictor of increased heart attack risk.

The only group of women at significant risk from the drugs are those who delay taking them for at least 10 years after menopause, experts said.

Hormone guidelines

The Food and Drug Administration recommends the following:

- Hormone therapy should be used at the lowest doses for the shortest duration needed to alleviate acute symptoms of menopause.
- It should not be used to prevent heart disease.
- It should be used to treat osteoporosis only in women who are at significant risk and cannot take non-estrogen medications.

Source: Food and Drug Administration

Iraqi city empties as U.S. forces comb area

About 40 fighters are killed, but residents say many others blended in with locals. Troops plan to wait them out.

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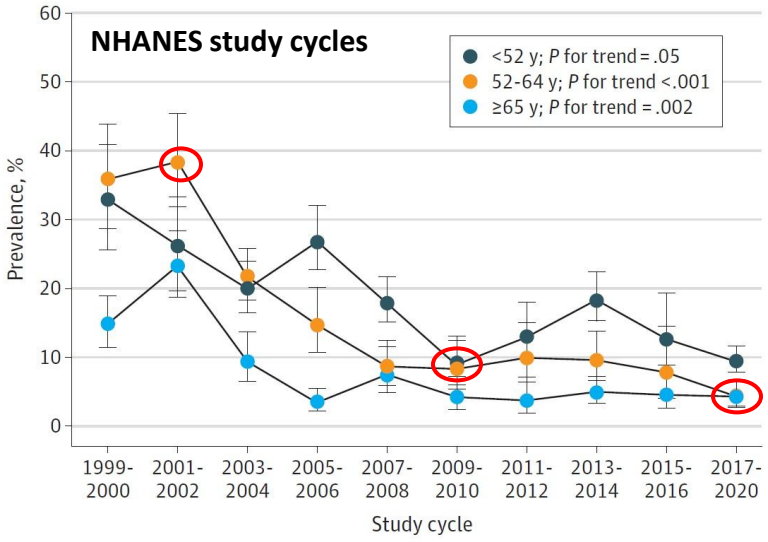
MHT: Where Are Now? Post-WHI Use in U.S. (1999-2020)



JAMA Health Forum. 2024;5(9):e243128

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Feb. 15, 2023

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MHT: Where Are We Now?
Contraindications

- known or suspected breast cancer
- active thromboembolic disease
- undiagnosed uterine bleeding
- active liver disease
- chronically impaired liver function
- endometrial cancer*

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MHT: Where Are We Now?
FDA-approved Indications

- hot flashes: 80 to 90 % reduction
- prevention of osteoporosis: maintains BMD, 50% reduction in fracture (WHI: 34-39% reduction)
- genitourinary atrophy: atrophic vaginitis, senile urethral syndrome

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MHT: Where Are We Now?
Non FDA-approved Indications

- **dermatologic changes of aging, i.e. wrinkling**
- **psychological symptoms (e.g. depression, anxiety, mood swings)**
- **cardioprotective effect (?)**

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MHT: Where Are We Now?
Evidence for Cardioprotective Effect

- **50 + epidemiological studies that supported a 50 % reduction in risk ***
- **biologically plausible:**
  - **favorable impact on lipids**
  - **antioxidant- reduced oxidized LDL**
  - **reversal of paradoxical vasoconstriction**

Maturitas 1998;30(1):19-26.

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MHT- WHI: E + P
Primary Prevention of CHD

- RCT primary prevention (JAMA 2002:288:321)
- 16,608 women, 50 to 79 yr (avg 63 yrs)
- mean F/U 5.2 yrs in E + P arm
- increased risk of CHD in E+P users with HR=1.29 (CI 1.02-1.63)

* N Engl J Med 2003;349:523-534

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MHT: WHI E + P Arm
C/V Events & Onset of Use

E + P Start Time	RR of CHD
< 10 yrs of menopause	0.88 (CI 0.54-1.43)
10 to 19 yrs of menopause	1.23 (CI 0.85-1.77)
> than 20 yrs of menopause	1.66 (CI 1.14-2.41)

Rossouw et al, JAMA 2007;297:1465-1477

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MHT- WHI: Unopposed E
Primary Prevention of CHD

- RCT primary prevention
- 10,739 women, 50 to 79 yr (avg 63.6 yrs)
- mean F/U 6.8 yrs in unopposed E arm
- no increased risk of coronary heart disease with HR=0.91 (CI 0.75-1.12)

JAMA 2004:291:1701

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WHI- Unopposed E
Primary Prevention of CHD

- RCT primary prevention

outcome No. of cases MI, CHD death, revascularization, angina by (annualized %)

age	CEE	placebo	HR
50-59	46 (0.35)	70 (0.56)	0.66 (0.45-0.96)
60-69	186 (1.11)	194(1.12)	0.98 (0.80-1.21)
70-79	148 (1.69)	141(1.58)	1.05 (0.84-1.23)

Arch Int Med 2006:166:357

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ELITE and CHD:
Primary Prevention of CHD

ELITE (Early vs Late Intervention Trial With Estradiol)

- **RCT launched in 7/04 by Nat'l Institute of Aging**
- **oral micronized estradiol (1 mg/d with intravaginal progesterone) given to women less than 6 yrs vs 10+ yrs from menopause**
- **primary outcomes: carotid artery intima- media thickness, coronary Ca+**

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ELITE and CHD:
Support for the "Timing Hypothesis"

- after median F/U of 5 years
- CIMT progression in early menopause
- (+) **estrogen:** 0.0044 mm/yr
- **placebo:** 0.0078 mm/yr ($p<0.008$)
- no difference in CIMT progression in late menopause women
- no difference in coronary Ca+ in any group

Hodis et al, NEJM 2016;374:1221-31

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Support for "Timing Hypothesis"

2015 Cochrane review "HT for preventing CVD in post-menopausal women":

TIMING OF MHT	ALL-CAUSE MORTALITY	CHD COMPOSITE
< 10 YRS AFTER MENOPAUSE OR AGE < 60 YEARS OF AGE	RR=0.70 (95% CI 0.52-0.95)	RR=0.52 (95% CI 0.29-0.96)
>10 YRS FROM MENOPAUSE OR > 60 YRS OF AGE	RR= 1.06 (95% CI, 0.95-1.18)	RR=1.07 (95% CI 0.96-1.20)

CHD composite: CVD death or non-fatal MI

Cochrane Database Syst Rev. 2015 Mar 10;2015(3):CD002229.

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WHI post-hoc Analysis:
ASCVD Risk for Women with Moderate to Severe VMS

MEDIAN F/U UP- CEE (1830*) 7.2 yrs, CEE+MPA (2043*)- 5.6 yrs

AGE	ASCVD Risk- CEE arm	ASCVD Risk- CEE + MPA arm
50-59 YRS	HR = 0.85 (95% CI 0.53-1.35)	HR = 0.84 (95% CI 0.44-1.57)
60-69 YRS	HR =1.31 (95% CI 0.9-1.90)	HR = 0.84 (95% CI 0.51-1.39)
70-79 YRS	HR = 1.95 (95% CI, 1.06-3.59)	HR = 3.22 (95% CI 1.36-7.63)

ASCVD: MI, CVA, hospitalization for angina, cardiac revascularization, PAD, carotid artery disease

* women with moderate to severe VMS

Rossouw J, JAMA Intern Med doi:10.1001/jamainternmed.2025.4510

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MHT: ? Cardioprotective Effect
Bottom Line

- **no role in the secondary prevention of coronary artery disease**
- **insufficient evidence for a role in the primary prevention of coronary artery disease**

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Potential Benefits of MHT

- **reduced risk of diabetes**
  - 35 % reduction (HERS, Ann Intern Med 2003)
  - WHI- E+P: HR=0.81 (CI 0.70-0.94)
    E: HR= 0.86 (CI 0.76-0.98)

Manson, JAMA 2024;331(20):1748

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Possible Benefits of MHT

- **reduced risk of colon cancer**
  - 35 to 40% reduction (Grodstein, Ann Intern Med 1989)
  - HR 0.80 (95% CI, 0.63-1.01) with E + P
  - HR 1.13 (95% CI, 0.85-1.51) with unopposed E

Manson, JAMA 2024;331(20):1748

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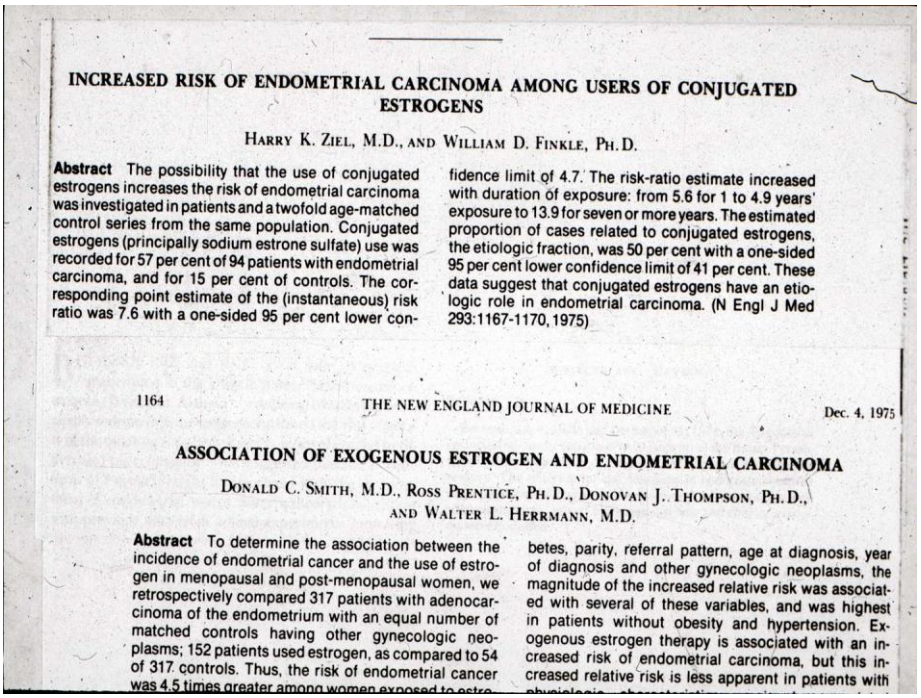

INCREASED RISK OF ENDOMETRIAL CARCINOMA AMONG USERS OF CONJUGATED ESTROGENS

HARRY K. ZIEL, M.D., AND WILLIAM D. FINKLE, PH.D.

Abstract The possibility that the use of conjugated estrogens increases the risk of endometrial carcinoma was investigated in patients and a twofold age-matched control series from the same population. Conjugated estrogens (principally sodium estrone sulfate) use was recorded for 57 per cent of 94 patients with endometrial carcinoma, and for 15 per cent of controls. The corresponding point estimate of the (instantaneous) risk ratio was 7.6 with a one-sided 95 per cent lower confidence limit of 4.7. The risk-ratio estimate increased with duration of exposure: from 5.6 for 1 to 4.9 years' exposure to 13.9 for seven or more years. The estimated proportion of cases related to conjugated estrogens, the etiologic fraction, was 50 per cent with a one-sided 95 per cent lower confidence limit of 41 per cent. These data suggest that conjugated estrogens have an etiologic role in endometrial carcinoma. (N Engl J Med 293:1167-1170, 1975)

1164 THE NEW ENGLAND JOURNAL OF MEDICINE Dec. 4, 1975

ASSOCIATION OF EXOGENOUS ESTROGEN AND ENDOMETRIAL CARCINOMA

DONALD C. SMITH, M.D., ROSS PRENTICE, PH.D., DONOVAN J. THOMPSON, PH.D., AND WALTER L. HERRMANN, M.D.

Abstract To determine the association between the incidence of endometrial cancer and the use of estrogen in menopausal and post-menopausal women, we retrospectively compared 317 patients with adenocarcinoma of the endometrium with an equal number of matched controls having other gynecologic neoplasms; 152 patients used estrogen, as compared to 54 of 317 controls. Thus, the risk of endometrial cancer was 4.5 times greater among women exposed to estro- betes, parity, referral pattern, age at diagnosis, year of diagnosis and other gynecologic neoplasms, the magnitude of the increased relative risk was associated with several of these variables, and was highest in patients without obesity and hypertension. Exogenous estrogen therapy is associated with an increased risk of endometrial carcinoma, but this increased relative risk is less apparent in patients with

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MHT: Where Are We Now?
ERT and Endometrial Cancer

- **link between unopposed estrogen and endometrial cancer established**
- **10 to 15 % annual incidence of adenomatous hyperplasia, 3-fold increased risk of cancer**
- **dose-duration effect: 8 X after 8 yrs**

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MHT: Where Are We Now?
Concerns Allayed Re Endometrial Ca

- **ERT-associated cancer tends to be localized and well-differentiated at time of diagnosis**
- **increased risk greatly offset by concomitant use of progestin agent**

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MHT: Where Are We Now?
ERT and Breast Cancer

- **most feared cancer among women**
- **most common cancer**
- **typical American female 50+ yrs**
  - 12% lifetime risk of developing it
  - 3% lifetime probability of dying from it

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MHT and Breast Cancer

Major Meta-analyses Prior to WHI

	RR(any use)	RR(long-term)
Armstrong(1988)	0.96	1.04
DuPont (1991)	1.08	--
Grady (1992)	1.00	1.25
Sternberg (1993)*	1.00	1.30
Sillero-Arenas (1992)	1.06	1.23
Colditz (1993)	1.02	1.23
Collaborative Grp (1997)	--	1.35

* 3.5 X risk if (+) fam hx

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MHT and Breast Cancer:

WHI: E + P Arm and Breast Cancer

- **RCT primary prevention of 16,608 women- ages 50-79 (avg 63 yr) mean F/U 5.2 yrs**
- **HR = 1.26 (CI 1.00-1.59)**
- **risk did not begin until after 4 yrs**
- **no effect of pre-existing risk factors: age, (+) family history, ethnicity, or BMI**

JAMA 2002;288:321-333

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Breast Cancer and E + P

Studies Suggesting Increased Risk

Study	RR
Colditz (1995)	1.41 (1.15-1.74)
Persson (1999)	1.7 (1.1-2.6)
Magnusson (1999)	1.68 (1.39-2.03)
NCI Study (2000)	1.4 (1.1-1.8)
Olsson (2003)	2.45 (1.61-3.71)
E3N* (2008)	1.66 (1.50-1.91)

* Breast Cancer Res Treat 2008;107:103

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MHT and Breast Cancer:

WHI: Unopposed E and Breast Ca

Stefanick et al:

- **RCT primary prevention of 10,739 women-ages 50-79 (avg 63.6 yr) mean F/U 7.1 yrs**
- **HR = 0.80 (CI 0.62-1.04) for invasive breast cancer**

JAMA 2006;295:1647

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MHT and Breast Cancer:
WHI: Health Outcomes After Stopping ET

Chlebowski et al:

- **RCT primary prevention of 10,739 women-intervention 7.2 yrs, cumulative F/U 20 yrs**
- **HR = 0.78 (CI 0.65-0.93) for breast cancer incidence**
- **HR = 0.60 (CI 0.37-0.97) for breast cancer mortality**

JAMA. 2020;324(4):369-380

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MHT and Breast Cancer:
Take-Home Lessons

- **HRT (E+P) users appear to be at higher risk of breast cancer**
- **risk appears confined to specific subsets:**

  extended use - RR=1.25-1.40 (WHI RR=1.26 after 4 yrs of use)
- **risk not reduced by progestin**
- **WHI: no higher risk using E alone Gradstein (7 yrs)**

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MHT: Where Are We Now?
Other Potential Risks

- **2-4 X risk DVT prior to WHI:**

WHI finding- 2 X (3.5 vs 1.7 per 1000 person-yrs)

- **2 X risk gallstones**
- **1.5 to 2 X risk ovarian cancer**
- **WHI finding: 1.37 X risk of stroke with E + P; 1.35 X risk with unopposed E ***

* JAMA 2013;310(13):1353-1368

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MHT: Where Are We Now?
2022 NAMS MHT Guidelines

- HT is the most effective Rx for VMS and GSM and has been shown to prevent bone loss and fracture
- benefits > risks among women with sx <60 yrs & within 10 yrs of menopause onset and have no contraindications
- risks of HT varies on the HT type, whether a progestogen is needed duration of use, timing of initiation, duration of use, and route of administration

GSM: genitourinary syndrome of menopause

Menopause 2022;29(7):767-94.

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Use of MHT and Risk of DVT
UK Research and CPRD Databases

Different types of HRT	Odds ratio (95% CI)
Oestrogen only oral HRT	
Conjugated equine oestrogen	1.49 (1.39 to 1.60)*
Estradiol	1.27 (1.16 to 1.39)*
Combined oral HRT	
Conjugated equine oestrogen	
Medroxyprogesterone	2.10 (1.92 to 2.31)*
Norgestrel	1.73 (1.57 to 1.91)*
Estradiol	
Medroxyprogesterone	1.44 (1.09 to 1.89)*
Dydrogesterone	1.18 (0.98 to 1.42)
Norethisterone	1.68 (1.57 to 1.80)*
Norgestrel/drospirenone	1.42 (1.00 to 2.03)
Transdermal HRT	
Estradiol	0.96 (0.88 to 1.04)
Combined estradiol	0.86 (0.73 to 1.01)
Other menopausal therapy	
Tibolone	1.02 (0.90 to 1.15)
Raloxifene	1.49 (1.24 to 1.79)*

BMJ. 2019 Jan 9;364:k4810

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MHT: Where Are We Now?
2022 NAMS MHT Guidelines

- personalization with shared decision-making remains key, with periodic reevaluation to determine an individual woman's benefit-risk profile
- benefits include impact on sleep, well-being, and QOL
- for treating sxs of GSM, consider low-dose vaginal ET

GSM: genitourinary syndrome of menopause

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Vaginal Estrogen Therapy

- 2025 AUA guidelines recommends for vaginal ET for GSM, recurrent UTI, OAB
- Danish nationwide nested case-control study of 56,642 women >45 yr with hx ischemic stroke- no higher risk of recurrence[3]
- meta-analysis by Beste et al[2], use of vaginal ET in women with history of breast cancer not associated with an increased risk of breast cancer recurrence, breast cancer-specific mortality, or overall mortality
- 2021 ACOG clinical consensus: if non-hormonal Rx ineffective in breast cancer survivor, low dose vaginal ET may be used after shared decision-making involving patient, gynecologist, and oncologist

1. AUA, J Urol 2025;214(3):242
2. Beste, Am J Ob Gyn 2025 ;Mar;232(3):262-270.e1.
3. Haddadan, Stroke. 2025 Aug 21. doi: 10.1161/STROKEAHA.125.050986
4. ACOG Committee Opinion, Obstet Gynecol 2021;138(6):950

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Vaginal ET in Breast Cancer Survivor
2022 ACOG Committee Opinion

"…If nonhormonal treatments have failed to adequately address symptoms, after discussion of risks and benefits, low-dose vaginal estrogen may be used in individuals with a history of breast cancer, including those taking tamoxifen. For individuals taking aromatase inhibitors (AIs), low-dose vaginal estrogen can be used after shared decision making between the patient, gynecologist, and oncologist."

Obstet Gynecol. 2021 Dec 1;138(6):950-960

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Vaginal Estrogen Therapy

TABLE 2. *Government-approved therapies for genitourinary syndrome of menopause in the United States and Canada*

Type	Composition	Product name	Commonly used starting dose	Commonly used maintenance dose	Typical serum estradiol level (pg/mL)
Vaginal creams	17B-estradiol 0.01% (0.1 mg active ingredient/g)	Estrace vaginal cream[a]	0.5-1 g/d for 2 wk	0.5-1 g 1-3 times/wk	Variable
	Conjugated estrogens (0.625 mg active ingredient/g)	Premarin vaginal cream	0.5-1 g/d for 2 wk	0.5-1 g 1-3 times/wk	Variable
	Estrone 0.1% (1 mg active ingredient/g)	Estragyn vaginal cream[b]		0.5-4 g/d, intended for short-term use; progestogen recommended	Variable
Vaginal inserts	17B estradiol inserts	Imvexxy[a]	4 or 10 μg/d for 2 wk	1 insert twice/wk	3.6 (4 μg) 4.6 (10 μg)
	Estradiol hemihydrate tablets	Vagifem Yuvafem	10 μg/d for 2 wk	1 tablet twice/wk	5.5
	Prasterone (DHEA) inserts	Intrarosa	6.5 mg/d	1 insert/d	5
Vaginal ring	17β estradiol	Estring	2 mg ring releases approx 7.5 μg/d	Replace ring every 90 days	8
Oral tablet	Ospemifene	Osphena[a]	60 mg/d	1 tablet by mouth/d	N/A

DHEA, dehydroepiandrosterone.

2020 NAMS GSM Position Statement

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MHT Case Study

JJ is a 55 y/o white G1P1 female seen for frequent, severe HF fatigue, joint pains, and poor sleep. LMP 1.5 years ago. PMHx and Fam Hx is unremarkable.

ROS menarche age 13; childbirth age 32. PE notable for BMI= 27 and BP 110/82 and urogenital atrophy.

Labs reveal TC 225, LDL 130 mg/dl, HDL 65 mg/dl, TG 80 mg/dl.

OTC drugs, including Estroven® and Vitamin E have not provided relief.

10-yr AHA CVD risk score= 1.4 %, 2.1% AHA PREVENT score

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Lifestyle Interventions for Hot Flashes

- avoiding triggers: hot drinks, caffeine, alcohol, hot or spicy foods, stress
- cooling techniques (e.g. use of hand or electric fans, ice pack under pillow, layered cotton clothing, lower room temperature.)
- regular exercise and yoga
- mind-body techniques (CBT, clinical hypnosis) *
- weight loss *

* Best evidence

NAMS Position Statement. Menopause 2023; 30:573

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Alternative Rx

- Black cohosh: mixed results
- Isoflavones : mixed results
- Pollen extract: no benefit
- Dong quai root: no benefit
- Wild yam: no benefit
- Maca: no benefit
- Evening primrose oil: no benefit
- Vitamin E: no benefit

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J Evid Based Integr Med. 2019; 24: 2515690X19829380; BJOG 2017 Mar 9; Nelson, JAMA 2006;295:2057;

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Trial with Gabapentin*

- **Guttoso et al**: menopausal women- gabapentin 900 mg/d produced 45 % reduction in hot flashes
- **Butt et al**: RCT of 197 women- gabapentin resulted in 51% reduction in hot flash scores
- **Reddy et al**: RCT of 60 women- gabapentin 2400 mg/day comparable to 0.625 mg CEE

*** off-label use**

Fertil Steril 2014;101:905–15
JAMA 2023;329(5):405

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Trial with SSRI or SNRI

- venlafaxine XR 75 mg/d produced 61 % reduction in hot flashes*
- duloxetine 30 to 120 mg/d- 56 to 62% improvement
- desvenlafaxine 100 mg/d- 64% reduction*
- paroxetine CR 12.5 to 25 mg/d produced 62 to 65 % reduction*
- FDA approved 6-28-13: Paroxetine mesylate (7.5 mg)

*** off-label use**

JAMA 2023;329(5):405

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Trial with Fezolinetant (Veozah®)

- selective neurokinin 3 receptor (NK3) antagonist
- FDA approved May 2023
- non-hormonal alternative to MHT
- efficacy: 64% reduction (45 mg dose), 58% (30 mg dose), 45% placebo at 12 weeks, respectively

JCEM 2023; 00:1-17
Lancet 2023;Apr 1:401(10382):1091-1102

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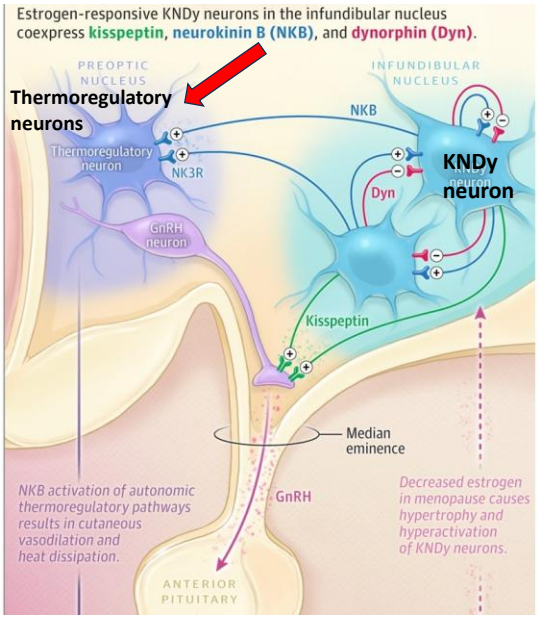

JAMA. Published online September 15, 2023. doi:10.1001/jama.2023.15965

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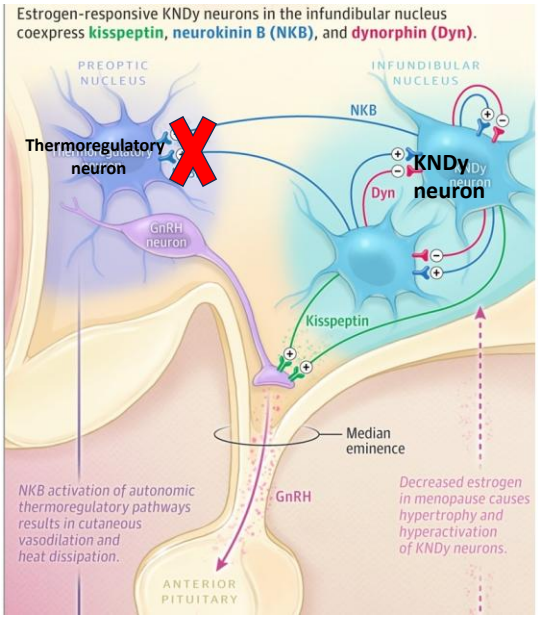

JAMA. Published online September 15, 2023. doi:10.1001/jama.2023.15965

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Fezolinetant Side Effects

Adverse reaction	FEZOLINETANT N=609	PLACEBO N=610
Abdominal pain	4.3 %	2.1 %
Diarrhea	3.9 %	2.6 %
Insomnia	3.9 %	2.3 %
Back pain	3.0 %	2.7 %
Hot flush	2.5 %	2.1 %
⇧ hepatic transaminase	2.3 %	1.1 %

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Trial with Fezolinetant (Veozah®)

- AST/ALT 3x ULN in 2% (30 mg) and 4% (45 mg)
- baseline liver enzymes
- liver enzymes at 3, 6, 9 months of use
- FDA recommends discontinuing if:
  - transaminitis 5X ULN or
  - transaminitis 3X ULN and bilirubin 2X ULN

Veozah® FDA prescribing information

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Elinzanetant (Lynkuet®)

- NK3 antagonist- > 60% experience 50% reduction VMS by week 4, >70% at week 12
- NK1 receptor blocker which improves sleep and reduces insomnia
- dose: 120 mg daily
- side effects: headache (7-9%), fatigue (5.5-7%), diarrhea (6%), dizziness (6%)
- no adverse impact on liver enzymes

Menopause 2023;30;239, JAMA 2024;332:1343, Menopause 2024;31:342

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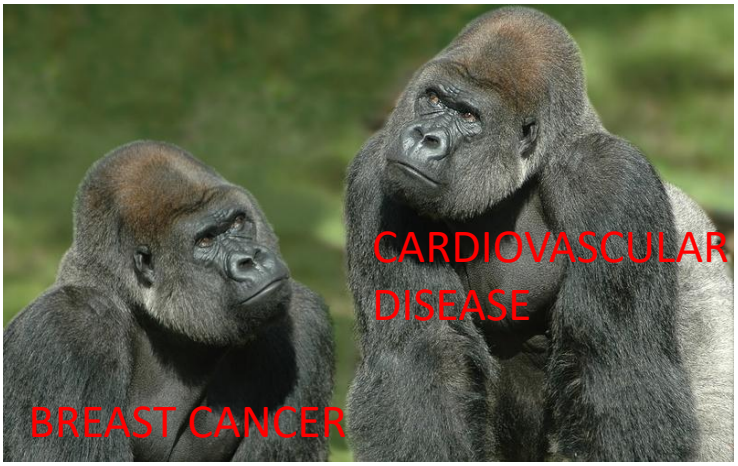
MHT: Where Are We Now?

What About MHT?



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WHI Post-hoc Analysis:

ASCVD Risk for Women with Moderate to Severe VMS

MEDIAN F/U UP- CEE (1830*) 7.2 yrs, CEE+MPA (2043*)- 5.6 yrs

AGE	ASCVD Risk- CEE arm	ASCVD Risk- CEE + MPA arm
50-59 YRS	HR = 0.85 (95% CI 0.53-1.35)	HR = 0.84 (95% CI 0.44-1.57)
60-69 YRS	HR =1.31 (95% CI 0.9-1.90)	HR = 0.84 (95% CI 0.51-1.39)
70-79 YRS	HR = 1.95 (95% CI, 1.06-3.59)	HR = 3.22 (95% CI 1.36-7.63)

ASCVD: MI, CVA, hospitalization for angina, cardiac revascularization, PAD, carotid artery disease

* **women with moderate to severe VMS**

Rossouw J, JAMA Intern Med doi:10.1001/jamainternmed.2025.4510

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CVD Risk Counseling and MHT

2023 ACC CVD in Women Committee & Endocrine Society

* **Avoid MHT in pts with history of MI or stroke, PAD, diabetes, AAA, CKD**

10 yr CVD Risk	< 5 Years from the Menopause	6-10 Years from the Menopause
Low (< 5%)	MHT OK	MHT OK
Intermediate (5 to 10 %)	MHT OK (choose transdermal)	MHT OK (choose transdermal)
High (> 10 %)	Avoid MHT	Avoid MHT

J Clin Endocrinol Metab 2015;100:3975-4011
Circulation 2023;147(7):597

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CVD Risk Counseling and MHT

2023 ACC CVD in Women Committee & Endocrine Soc

10 yr CVD Risk	< 5 Years from the Menopause	6-10 Years from the Menopause
Low (< 5%)	**MHT OK**	**MHT OK**
Intermediate (5 to 10 %)	MHT OK (choose transdermal)	MHT OK (choose transdermal)
High (> 10 %)	Avoid MHT	Avoid MHT

J Clin Endocrinol Metab 2015;100:3975-4011
Circulation 2023;147(7):597

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CVD Risk Counseling and MHT

2023 ACC CVD in Women Committee & Endocrine Society

10 yr CVD Risk	< 5 Years from the Menopause	6-10 Years from the Menopause
Low (< 5%)	MHT OK	MHT OK
Intermediate (5 to 10 %)	**MHT OK (transdermal)**	**MHT OK (transdermal)**
High (> 10 %)	Avoid MHT	Avoid MHT

J Clin Endocrin Metab 2015;100:3575
Circulation 2023;147(7):597

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CVD Risk Counseling and MHT

2023 ACC CVD in Women Committee & Endocrine Society

10 yr CVD Risk	< 5 Years from the Menopause	6-10 Years from the Menopause
Low (< 5%)	MHT OK	MHT OK
Intermediate (5 to 10 %)	MHT OK (choose transdermal)	MHT OK (choose transdermal)
High (> 10 %)	**Avoid MHT**	**Avoid MHT**

* Avoid in pts with history of MI or stroke, PAD, diabetes, AAA, CKD

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Breast Cancer Risk
Gail Model Score

- **NCI:** http://www.cancer.gov/bcrisktool/Default.aspx
- **7- question tool for assessing 5-yr risk for breast cancer: age, ethnicity, menarche, age at first birth, fam history, hx breast bx, and hx ductal CIS or lobular CIS**
- **low-average risk = < 1.66 %**
- **case study score: 1.6 %**

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Breast Cancer Counseling and MHT
Endocrine Society

Risk Category	5-year risk for breast cancer	Suggested approach
Low	< 1.67 %	MHT OK
Intermediate	1.67 to 5 %	Caution
High	> 5%	Avoid

J Clin Endocrinol Metab 2015;100:3975-4011

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Breast Cancer Counseling and MHT
Endocrine Society

Risk Category	5-year risk for breast cancer	Suggested approach
Low	**< 1.67 %**	**MHT OK**
Intermediate	1.67 to 5 %	Caution
High	> 5%	Avoid

J Clin Endocrinol Metab 2015;100:3975-4011

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Breast Cancer Counseling and MHT
Endocrine Society

Risk Category	5-year risk for breast cancer	Suggested approach
Low	< 1.67 %	MHT OK
Intermediate	**1.67 to 5 %**	**Caution**
High	> 5%	Avoid

J Clin Endocrinol Metab 2015;100:3975-4011

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Breast Cancer Counseling and MHT
Endocrine Society

Risk Category	5-year risk for breast cancer	Suggested approach
Low	< 1.67 %	MHT OK
Intermediate	**1.67 to 3 %**	**Caution**
High	> 5%	Avoid

J Clin Endocrinol Metab 2015;100:3975-4011

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Breast Cancer Counseling and MHT
Endocrine Society

Risk Category	5-year risk for breast cancer	Suggested approach
Low	< 1.67 %	MHT OK
Intermediate	1.67 to 5 %	Caution
High	**> 5%**	**Avoid**

J Clin Endocrinol Metab 2015;100:3975-4011

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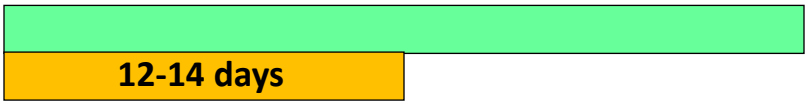
MHT: Where Are We Now?

MENOPAUSE HORMONE THERAPY REGIMENS

Unopposed estrogen

Continuous estrogen/ cyclic progestin



Continuous combined HRT

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TABLE 2 | Menopausal hormone therapy by formulation and route available in the United States (16).

Oral Estrogen

Formulation	Brand Name	Dose (mg/d)
Conjugated	Premarin	0.3, 0.45, 0.625, 0.9, 1.25
Synthetic conjugated	Cenestin	0.3, 0.45, 0.625, 0.9, 1.25
Esterified	Menest	0.3, 0.625, 1.25, 2.5
17β-Estradiol	Estrace, Gynodiol, Innofem, Generics	0.5, 1.0, 2.0
Estradiol Acetate	Femtrace	0.45, 0.9, 1.8
Estropipate	Ortho-Est, Ogen, Generics	0.625(0.75 estropipate), 1.25 (1.5), 2.5 (3.0), 5.0 (6.0)

Transdermal Estrogen

Formulation	Brand Name	Dosage (mg)
17β-estradiol matrix patch	Alora	0.025, 0.05, 0.075, 0.1 twice/wk
	Climar	0.025,0.0375, 0.05, 0.075, 0.1 once/wk
	Esclim	0.025,0.0375 0.05, 0.075, 0.1 twice/wk
	Estradot	0.025,0.0375 0.05, 0.075, 0.1 twice/wk
	Fempatch	0.025 once/wk
	Menostar	0.014 once/wk
	Minivelle	0.025, 0.0375 0.05, 0.075, 0.1 twice/wk
	Vivelle	0.025,0.0375, 0.05, 0.075, 0.1 twice/wk
	Vivelle-Dot	0.025,0.0375, 0.05, 0.075, 0.1 twice/wk
	Generics	0.05, 0.1 once or twice/wk
17β-estradiol reservoir patch	Estraderm	0.05, 0.1 twice/wk
17β-estradiol transdermal gel	EstroGel	0.035/d
	Elestrin	0.0125/d
	Divigel	0.25, 0.5, 1.0 g/d
17β-estradiol topical emulsion	Estrasorb	0.05/d (2 packets)
17β-estradiol transdermal spray	Evamist	0.021/90 μL/d (up to 1.5/90 μL/d)

Front Endocrinol 2021;March 26:12:564781

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Estrogen Dosing in MHT

ESTROGEN	Ultra-low	Low dose	Standard	High
CEE		0.3-0.45 mg	0.625 mg	1.25 mg
Oral 17-beta estradiol	0.25 mg	0.5 mg	1 mg	2 mg
Transdermal estradiol	0.014 mg	0.025 mg	0.05 mg	0.1 mg

2015 ACOG Technical Bulletin ;
British Menopause Society Guidelines- April 2024
https://thebms.org.uk/publications/bms-guidelines/management-of-unscheduled-bleeding-on-hormone-replacement-therapy-hrt/

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Progestogen Dosing in MHT

	CONTINUOUS	CYCLIC (days 12-14)
medroxyprogesterone acetate	2.5-5 mg daily	5-10 mg/day
micronized Progesterone	100 -200 mg qhs	200 mg qhs 100 mg in AM, 200 mg in PM
norethindrone acetate	0.35 mg daily	1 mg daily

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Progestin Use in MHT and Breast Cancer Risk
UK Clinical Practice Research Datalink (1995-2015)

CASE CONTROL STUDY (43,183 cases, 431,930 controls) MHT
O.R. = 1.12 (95% CI 1.09-1.15)

MHT EXPOSURE	ADJUSTED O.R.	95% C.I.
No estrogen	O.R. = 1 .0	REFERENCE
Animal-derived estrogen	O.R. = 1.01	0.96-1.06
Synthetic estrogen	O.R. = 1.04	1.00-1.09
No progestin	O.R. = 1.0	REFERENCE
Synthetic progestin	O.R. = 1.28	1.22-1.35
Bioidentical progestin	O.R. = 0.99	0.55-1.79

Obstet Gynecol 2022;139:1103

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Low Dose Estrogen

Benefits:

- **reduced risk for thrombosis**
- **effective for reducing hot flashes**
- **effective for genitourinary atrophy**
- **prevents loss of BMD**
- **reduced likelihood of bleeding**

Obstet Gynecol 2014;123(1):202
Fertil Steril 2014;101:905–15

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MHT: Where Are We Now?
Potential Estrogen Side Effects

- nausea, vomiting
- breast tenderness
- edema, fluid retention
- bloating
- headache

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Low Dose MHT

Low-dose systemic ET:

- 0.3 mg oral CE
- 0.5 mg oral micronized 17ß-estradiol
- 0.025 mg 17ß-estradiol patch

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Low Dose MHT

Low-dose progestin agent

- **1.5 mg oral MPA**
- **0.5- 1 mg oral norethindrone acetate**
- **50-100 mg micronized progesterone**

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MHT: Where Are We Now?
Potential Progestin Side Effects

- **depression, fatigue**
- **anxiety, irritability**
- **weight gain**
- **breast tenderness**
- **headache**
- **reduction HDL, increase LDL**

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Switch to Conjugated Estrogen/Bazedoxifene

- **Combination product**
- **FDA approved in 2013 for treatment of VMS and osteoporosis**
- **Bazedoxifene is a SERM**
  - preserves BMD, reduces vertebral and non-vertebral fractures
  - increased risk of DVT
  - reduces endometrial thickness

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Switch to LNG-IUS

- **Represents off-label use in U.S.**
- **Studied in Europe**
- **Both LNG-IUS (52 mg) and LNG-IUS (13.5 mg) effective but more data for the former**

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Bioidentical Hormones

- hormones chemically identical to those made in the body
- started as marketing term and used to refer to non-FDA approved formulations from compounding pharmacies
- compounded HT not standardized or studied, variable purity and potency and lack safety and efficacy data
- variable bioavailability makes underdosage and overdosage possible
- "natural" hormones available in FDA approved products-singly or in combination

Menopause 2022;29(7):767

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Risk of CHD After 70 Years
WHI: Use of MHT for Severe VMS

MHT regimen	HR of CHD
CEE + 2.5 mg MPA	5.79 (CI 1.29-25.97)
CEE unopposed	4.34 (CI, 1.43-13.14)

Manson et al, JAMA 2013;310:1353-68

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WHI Mortality Outcomes
18 Years Cumulative Follow Up

- observational F/U of 27,347 women participating in WHI
- CEE + MPA(n=8506) for 5.6 yrs (median) vs placebo (n=8102) or CEE alone (n=5310) vs placebo (n=5429) for 7.2 years (median)
- deaths: 1,088 during intervention phase,
- 6,401 during post-intervention F/U

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

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WHI Cause-Specific Mortality
18 Years Cumulative Follow Up

	ALL CAUSE MORTALITY HR (95% CI)	CVD MORTALITY HR (95% CI)	BREAST CA MORTALITY HR (95% CI)
CEE + MPA vs PLACEBO	1.02 (0.96-1.08)	1.03 (0.92-1.15)	1.44 (0.97-2.15)
CEE alone vs PLACEBO	0.94 (0.88-1.01)	0.94 (0.88-1.01)	0.55 (0.33-0.92)

Manson , JAMA 2017: 318(10):927-938

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Menopause HT: After WHI

- MHT remains the most effective treatment for sxs of the menopause
- when prescribed for short-term relief of symptoms, benefits > risks
- should not be used for primary prevention of disease (JAMA 2022;328:1740)
- long-term use of E + P must be regularly re-evaluated for risks > benefits

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Menopause HT: After WHI

"Opinion is like a pendulum and obeys the same law. If it goes past the centre of gravity on one side, it must go a like distance on the other; and it is only after a certain time that it finds its true point at which it can remain at rest"

Schopenhauer

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MH is a 56-year-old female being seen by you for hot flashes. Her hot flashes occur frequently at night and disrupts her sleep. She reports problems with fatigue and memory issues during the day which has impaired her function at work as well as me. Her past medical history is notable only for a TAH 8 years ago for endometriosis. She expresses an interest in MHT but is concerned about associated risks.

Concern Regarding Which One of the Following Would Be the Least Appropriate for Her to Avoid MHT?

A. Risk of myocardial infarction
B. Risk of stroke
C. Risk of breast cancer
D. Risk of developing type 2 diabetes

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In a Menopausal Patient with a Peanut Allergy, Which One of the Following MHT Regimens Should Be Avoided?

A. Conjugated estrogen and Provera
B. Compounded estradiol and Provera
C. 17β-estradiol and Prometrium
D. 17β-estradiol plus compounded progesterone

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