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BMS Meeting

Is there again/still a place for Menopause Hormone Therapy for osteoporosis treatment?

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Assessment and management of osteoporosis in AN

• Encouraged to gain weight.

• Recovering a near-normal or normal BMI (between 18-25 kg/m²) will generally help to recover a normal reproductive functioning, which can be assessed by a regular menstrual cycle (not using hormone therapy).

• Restoration of body weight will also improve BMD although a complete catch-up does not always occur.

Assessment and management of osteoporosis in AN

- In addition, AN patients should take adequate calcium (e.g., 1200 mg) and vitamin D (e.g., 800 IU) daily, from diet and supplements.

Assessment and management of osteoporosis in AN

• Although one may be tempted to restore menstruation in these patients using oral contraceptives.
• High-dose estrogen-progestin contraception is not an effective treatment.
• Several studies have failed to observe a protective effect of the “pill” even when containing 50µg ethynilestradiol.

Assessment and management of osteoporosis in AN

• MHT such as 100 µg transdermal 17-beta-estradiol with cyclic micronized progesterone in adolescents resulted in BMD gains at the spine and hip compared with placebo, though the therapy did not restore BMD to normal.

Physiologic estrogen replacement increases bone density in adolescent girls with anorexia nervosa.
Effect of early menopause on bone mineral density and fractures.

- Early menopause is a risk factor for osteoporosis. Women with an early menopause should have bone density testing performed within 10 years of menopause so that osteopenia or osteoporosis will be diagnosed early and appropriate anti-resorptive therapy initiated.

Bone Mineral Density in Estrogen-Deficient Young Women

BMD (g/cm²) of women with POI (n = 353), concurrent controls (n = 70), & NHANES controls (n = 353). *, P < 0.001 compared with either control group indicates statistical significance. The concurrent and NHANES control groups did not differ significantly (P = 0.07). Multiple regression analysis was used to adjust for the effect on bone density of age, BMI, and race. Error bars represent sem. Vaishali et al J Clin Endocrinol Metab. 2009 Jul; 94(7): 2277–2283.
Premature and early menopause

• Premature (before 40 years) and early menopause (before 45 years), whether natural or induced, is associated with increased morbidity & mortality, when women are untreated with MHT.
• Several recent meta-analyses reported in particular increased cardiovascular morbidity-mortality (Grade 1C)

Hypoestrogenism caused by hypogonadism, POI, or premature surgical menopause without contraindications

- HT is recommended until at least the median age of menopause (52 y). (Level II)
- (Based on limited or inconsistent scientific evidence.)

- NAMS guidelines 2017, Belgian Menopause Society guidelines 2017
Indications of MHT for osteoporosis

- Anorexia
- POI /POF
- Bilateral oophorectomy
- Menopause at an early age
Mrs V

• 53 years old
• Has never had fractures.
• Has moderate –severe VMS
• BMD : -2.0 T-score
• Mother : Osteoporosis
• Frax :10 yr: Major fracture: 5.8%, Hip 0.8%
Mrs T

- 58 years old
- Has never had fractures.
- BMD : -2.7 T-score
- Mother : Osteoporosis
- Frax :10 yr: Major fracture: 8.1%, Hip 1.4%
Bone mineral content in postmenopausal women during three years of treatment: the first two years with either placebo (red) or with estradiol cyclically combined with a small dose of norethisterone (blue); the women were then rerandomized to continued therapy or the other regimen in the third year. Estrogen therapy increased bone density when given as initial therapy (upper curve) and after two years of placebo. Replacement of estrogen with placebo led to a decline in bone density.

Bone sparing doses of commonly used preparations

• Estradiol 2 mg
• Estradiol valerate 2 mg
• CEE 0.625 mg
• Transdermal estradiol 0.05 mg
• estradiol cream 1.5-3 mg

• Adapted from Guidelines for diagnosis and management of osteoporosis 1997 Ost Int
HRT and Prevention of Nonvertebral Fractures: A Meta-analysis of Randomized Trials

- RR = 0.73 (95% CI 0.56-0.94; \( P = .02 \)).
- younger than 60 years (RR, 0.67; 95% CI, 0.46-0.98; \( P = .03 \)).
- > 60 years or older: RR, 0.88; 95% CI, 0.71-1.08; \( P = .22 \)).
- Hip and wrist: (RR, 0.60; 95% CI, 0.40-0.91; \( P = .02 \)),
- < 60 years (RR, 0.45; 95% CI, 0.26-0.79; \( P = .005 \)).

_Torgerson, Bell-Syer JAMA 2001_
In the Women's Health Initiative, combined estrogen-progestin replacement therapy was associated with significant reduction in hip fracture (five fewer hip fractures per 10,000 person-years; HR 0.7, unadjusted 95% CI 0.4-1.0).

HR: hazard ratio.

WHI: E+P per 10,000 woman years

- 46 fractures
+ 8 breast cancer
+ 9 stroke
+ 12 DVT, deep, + 9 pulmonary embolism

Other events that increased with estrogen + progestin treatment included deaths from lung cancer, gallbladder disease, probable dementia and urinary incontinence

Uptodate

• More subtle analyses
• New studies
  • Keeps
  • Elite
  • .....
Perspective Menopause Management — Getting Clinical Care Back on Track

JE Manson, AM Kaunitz
N Engl J Med
March 3, 2016

Benefits and Risks of the Two Hormone-Therapy Formulations Evaluated in the Women’s Health Initiative.

Results are shown for the two formulations, conjugated equine estrogens (CEE) alone or in combination with medroxyprogesterone acetate (MPA), for women 50 to 59 years of age. 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 1000 women over 5 years. Data are from Manson et al.³
WHI clinical trials: interaction of calcium and vitamin D with hormone therapy

Robbins et al. Menopause. 2014 Feb

Figure 2.
Cumulative hazards for the incidence of hip fracture by HT and CaD randomization. Cumulative hazard functions of hip fracture that allow for randomization into the CaD trial as a time-dependent variable.
Adapted use of MHT & other regimens

- Lower dosage of estrogens
- Other progestins
  - Better safety profile
- Vaginal estrogen or SERMS
- Development of new products
  - SERMS + estrogens (CEE+BAZO)
Efficacy of 1mg E2 + 0.5mg NETA on BMD

Adapted from McClung et al 1998
Endogenous hormones and risk of Hip & vertebral fractures among older women

hip fracture risk : (E2 <5 pg/ml)

Vtx fracture risk : (E2 <5 pg/ml)

Cummings et al NEJM1998
low-dose MHT & fractures

• Neither (oral CEE 0.3 mg; oral 17b-estradiol 0.5 mg; or estradiol patch 0.025mg) nor ultralow-dose (estradiol patch 0.014mg) therapy has been shown to reduce fracture risk, although no studies have been adequately powered for this endpoint.

• NAMS Consensus 2017
Breast cancer, endometrial cancer, and cardiovascular events in participants who used vaginal estrogen in the WHI Observational Study.

- Among women with an intact uterus, the risks of stroke, invasive breast cancer, colorectal cancer, endometrial cancer, and pulmonary embolism/deep vein thrombosis were not significantly different between vaginal estrogen users and nonusers, whereas the risks of CHD, fracture, all-cause mortality, and global index event (GIE) were lower in users than in nonusers (GIE adjusted hazard ratio 0.68, 95% CI 0.55-0.86).

- Among hysterectomized women, the risks of each of the individual GIE components and of the overall GIE were not significantly different.

Breast cancer, endometrial cancer, and cardiovascular events in participants who used vaginal estrogen in the WHI Observational Study.


FIG. 2. Hazard Ratio (HR) and 95% Confidence Interval (CI) for Global Index Events (GIE) and Components by Vaginal Estrogen (VE) Use Overall and by Hysterectomy Status. VE includes vaginal cream or vaginal tablet. VE and hysterectomy status were included in the model as time-varying covariates. Global Index Event (GIE) is defined as time to first coronary heart disease, breast cancer, stroke, pulmonary embolism, hip fractures, colorectal cancer, endometrial cancer, or death. Analysis for endometrial cancer was not conducted in participants with hysterectomy or in the overall analytic sample. Rate are crude rates per 1000 person-years (N = 45,663). Model 1 is adjusted for age, education, past estrogen use, history of cancer before study baseline, history of cardiovascular disease before study baseline, history of deep vein thrombosis or pulmonary embolism before study baseline. Model for overall analytic sample also includes hysterectomy status (N = 45,251). Model 2 was adjusted for variables in Model 1 and race/ethnicity, baseline body mass index, baseline diagnosis of diabetes, baseline physical activity (total MET-hours/week), hypertension, Gail breast cancer risk score, fracture after age 55 prior to study enrollment, smoking, income, and alcohol use (servings/week) (N = 36,629).
HRT & hip fracture risk: A population based case (n=1327) - control study (n=3262)

Never users

Last use <=1 yr (total >5 yr)

Last use 1-5 yr (total >5 yr)

Last use >5 yr (total >5 yr)

Odds Ratio of hip fracture from Michaëlsson et al BMJ 1998
Changes in bone density and turnover after alendronate or estrogen withdrawal.

- 1,609 postmenopausal women 45 - 59 years using ALN, placebo, or E+P (CEE+MPA / E2+NETA).
- 1/3 after year 2 and 1/3 after year 4 switched to placebo,
- Women using E+P in years 1 - 4 were followed off therapy in years 5 - 6.
- BMD steadily decreased in the placebo group during all 6 years.
- BMD increased during the first 4 years when ALN or E+P.
- During years 5 and 6, BMD decreased L2-L4 : \(-2.42\%\) (95% CI = \(-4.10, -0.74\)) and total hip \(-1.09\%\) (-2.60, 0.41) in the group previously treated with ALN for 4 years and L2-L4 [-7.69\% (-8.96, -6.41)] and total hip [-5.16\% (-6.30, -4.01)] among those using E+P for 4 years
The WHI HT Trials: Update and Overview of Health Outcomes During the Intervention and Post-Stopping Phases

• Hip fracture

• Intervention phase: Women in the CEE+MPA and CEE, compared to placebo, groups had statistically significant 33% reductions in hip fracture

• Post-intervention and cumulative follow-up: Post-intervention, the risk reductions were attenuated in both trials but a significant fracture benefit persisted at 13 years for CEE+MPA (HR=0.81 [0.68–0.97]).

• Stratified analyses: Results in the CEE trial were more favorable for women with greater time since menopause

• Manson et al *JAMA*. 2013 October 2; 310(13): 1353–1368.
No Increase in Fractures After Stopping Hormone Therapy: Results From the Women's Health Initiative.

- Examine fractures after discontinuation of HT.
- 2 RCT (CEE+ MPA) / CEE alone) WHI participants (N = 15,187) who continued active HT or placebo through the intervention period and who did not take HT in the post-intervention period.
- Hip fractures were infrequent (~2.5 / 1000 person-years); this finding was similar between trials and in former HT and placebo groups.
- CEE + MPA trial: No difference in total fractures HR= 0.97; 95% CI, 0.87 - 1.09; P = 0.63)
- CEE-alone trial: higher total fractures in former placebo users (36.9/1000 person-years vs former active group 31.1/1000 person-years), residual benefit of CEE (HR, 0.85; 95% CI, 0.73 to 0.98; P = 0.03).
From: No Increase in Fractures After Stopping Hormone Therapy: Results From the Women’s Health Initiative
J Clin Endocrinol Metab | Copyright © 2017 by the Endocrine Society
Key points

• For women with VMS aged younger than 60 years or who are within 10 years of menopause onset, HT (ET, EPT, or CEE combined with bazedoxifene) is probably the most appropriate bone-active therapy in the absence of contraindications.
Indications of MHT for osteoporosis

- Anorexia
- POI /POF
- Bilateral oophorectomy
- Menopause at an early age
- VSM + Osteoporosis /osteopenia in < 60 years
Mrs V : Her Complaint

- 65 years old
- Has fractured her wrist recently.
- 55 kg 165 cm
- BMD : -3.0 T-score
- Mother : Osteoporosis
- Frax : 1O yr: Major fracture: 25%, Hip 6.7%
  - Using MHT
  - Not using MHT
FIG. 1. Absolute risks of health outcomes by 10-year age groups in the Women’s Health Initiative Hormone Therapy Trials during the intervention phase. CEE, conjugated equine estrogens; MPA, medroxyprogesterone acetate. From Manson et al.© Reproduced with permission of the American Medical Association ©American Medical Association. All rights reserved.
Key points

• When alternate osteoporosis therapies are not appropriate or cause AEs, the extended use of HT is an option for women who are at high risk of osteoporotic fracture.

• The decision to stop HT should be made on the basis of extraskeletal benefits and risks.

• NAMS guidelines 2017
Conclusions

- MHT prevents bone loss in healthy postmenopausal women, with dose-related effects.
- Unless contraindicated, women with premature menopause who require prevention of bone loss are best served with HT until the average age of menopause, when treatment may be reassessed.
Conclusions

• MHT effectively prevents post-menopause osteoporosis and fractures.
• – It is possible that bone protection dissipates rapidly after HT discontinuation, but no rebound in fracture risk has been found.
• -It is also possible that some benefit lasts for several years
Conclusions

• For women with VMS aged younger than 60 years or who are within 10 years of menopause onset, HT is probably the most appropriate bone-active therapy in the absence of contraindications.

• After that age, HT might not be appropriate but the decision to stop / initiate HT should always be made on the basis also of extraskeletal benefits and risks.