Menopause and Hormone Therapy

Clinical specialty: Obstetrics and Gynecology
Intended users: Physicians and students
Source of Evidence: The Cochrane Library and DARE

JC Objective
To discuss the evidence for the management of Menopause and Hormone Therapy

Definitions
1. Postmenopausal women:
   a. women with spontaneous menopause and amenorrhea for >12 months.
   b. women with surgical menopause (bilateral oophorectomy)
2. Perimenopausal women: women with menopausal symptoms who have not yet had their final menstrual period.

Clinical features
1. vasomotor menopausal symptoms (hot flushes and night sweats)
2. Genitourinary
   a. Vaginal atrophy, dryness, dyspareunia
   b. urinary incontinence
   c. pelvic organ prolapse
3. General
   a. Quality of life
   b. Bone mineral density (osteoporosis). Incidence of fractures (vertebral, hip)
   c. Coronary events (MI or death)
   d. Stroke and transient ischemic attacks
   e. Dementia and diminished cognitive function
   f. Weight and body fat distribution

Note
The perception of the patient is always relevant. A very small absolute risk increase in breast cancer may be more important to women than the small ARI in VTE in women receiving HRT

General management
1. Fasting lipid profile, blood glucose, mammography and DEXA bone densitometry.
2. Lifestyle modifications: cessation of smoking, diet, and the maintenance of appropriate BMI, exercise and stress reduction.
3. Medical treatment of dyslipidaemias, hypertension and diabetes should be optimal
4. All patients should be re-evaluated annually
HT

1. **Estrogen therapy alone (ERT)**
   a. Conjugated equine estrogen (CEE): 0.625 or 1.25 mg daily
   b. 17-beta estradiol: 1 mg or 2 mg
   c. Transdermal estradiol patches

2. **Combined regimens: estrogen plus progestogen (EPT)**
   a. Continuous combined regimens:
      i. CEE 0.625 mg plus MPA 2.5 mg daily or CEE 2.5 mg plus MPA 10 mg daily
      ii. Estradiol 2 mg with 1 mg norethisterone daily
   b. Combined sequential regimens:
      i. CEE 0.625 mg daily with MPA 10 mg days 1 to 12
      ii. CEE 0.625 mg daily with micronized progesterone 200 mg days 1 to 12
      iii. Estradiol daily with MPA 5 mg for 12 days once a year
      iv. Estradiol daily with norethisterone 1 mg days 13 to 22
      v. Estradiol daily with dydrogesterone 5 or 10 mg days 14 to 28

3. **Routes:** Oral, transdermal, Vaginal

**Summary of the Evidence**

**Vasomotor menopausal symptoms**

1. Oral HT is highly effective in alleviating hot flushes, night sweats, and associated sleep disorders.
2. Significant reduction in the frequency and severity:
   a. 75% reduction in frequency (95% CI 64.3 to 82.3) for HT relative to placebo.
   b. Symptom severity significantly reduced compared to placebo.
      OR 0.13, 95% CI 0.07 to 0.23

**Vaginal symptoms: estrogen cream vs moisture gel**

1. Vaginal dryness index (improvement): MD (95% CI) 4.46 [2.76 to 6.16]
2. Vaginal pH (decreased): MD (95% CI): -0.36 [-0.52 to -0.21]

**Fragility fractures**

1. **Hip fractures**
   a. CEE 0.625 mg for **7.1 yrs**: RR 0.64 (0.45 to 0.93): 5 fewer per 1000
   b. CEE 0.625 mg + MPA 2.5 mg for 1 yr: RR 0.64 (0.26 to 1.57)
   c. CEE 0.625 mg + MPA 2.5 mg for mean **5.6 yrs**: RR 0.68 (0.48 to 0.97): 3 fewer per 1000

2. **Vertebral fractures**
   a. CEE 0.625 mg for **6.8 yrs**: RR 0.62 (0.42 to 0.93): 4 fewer per 1000
   b. CEE 0.625 mg + MPA 2.5 mg for **5.6 yrs**: RR 0.65 (0.44 to 0.97): 3 fewer per 1000

3. **All clinical fractures**
   a. CEE 0.625 mg for **7.1 yrs**: RR 0.73 (0.65 to 0.8): 38 fewer per 1000
   b. CEE 0.625 mg + MPA 2.5 mg for 1 year: RR 0.69 (0.46 to 1.02)
   c. CEE 0.625 mg + MPA 2.5 mg for **5.6 yrs**: RR 0.78 (0.71 to 0.85): 24 fewer per 1000

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Death

No improvement

Decline in global cognitive function

NO improvement

Coronary disease

CEE 0.625 mg for 7.1 yrs: RR 0.95 (0.78 to 1.14)
CEE 0.625 mg + MPA 2.5 mg for 1 yr: RR **1.89 (1.15 to 3.1)**
CEE 0.625 mg + MPA 2.5 mg for 5.6 yrs: RR 1.22 (0.98 to 1.51)

Stroke

CEE 0.625 mg for **7.1 yrs**: RR **1.35 (1.08 to 1.7)**: 8 more per 1000
CEE 0.625 mg + MPA 2.5 mg for 1 yr: RR 0.95 (0.49 to 1.86)
CEE 0.625 mg + MPA 2.5 mg for **5.6 yrs**: RR **1.34 (1.05 to 1.72)**: 4 more per 1000

VTE (DVT or PE)

CEE 0.625 mg for up to 2 yrs: RR 2.22 (1.12 to 4.39): 3 more per 1000
CEE 0.625 mg + MPA 2.5 mg for 1 yr: RR 4.28 (2.49 to 7.34): 5 more per 1000

Gallbladder disease requiring surgery

1. Estrogen-only HT: RR 1.75 (1.4 to 2.19): 19 more per 1000
2. Combined continuous HT for 5.6 yrs: RR 1.64 (1.3 to 2.06): 10 more per 1000

Cancer

1. Breast cancer:
   a. Estrogen only: not increased
   b. Combined Continuous: CEE 0.625 mg + MPA 2.5 mg
      i. for up to 2 yrs: not increased
      ii. for 5.6 yrs: RR 1.26 (1.02 to 1.56): 5 more per 1000
   c. Death from breast cancer: not increased
2. Colorectal cancer
   a. CEE 0.625 mg + MPA 2.5 mg for 5.6 yrs: RR 0.62 (0.43 to 0.89): 3 fewer per 1000
3. Endometrial cancer: not increased with combined regimens
4. Ovarian cancer: not increased

Tibolone

1. Significantly reduced hot flushes and increased BMD in postmenopausal women.
2. Long-term effects of tibolone, in reducing fractures, breast cancer and CVD, are still unknown.

Raloxifene

1. RR of vertebral fracture of 0.65 (95% CI 0.53 to 0.79),
2. RR of hip fracture, wrist fracture, and other non-vertebral fractures: evidence of No difference
3. Protects against breast cancer: RR at 4 years for all types of breast cancer 0.38 (95% CI 0.24 to 0.58), and that for invasive breast cancer 0.28 (95% CI 0.17 to 0.46).

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4. Adverse events
   a. VTE (three-fold increased risk).
   b. higher incidences of hot flushes, arthralgia, dizziness, leg cramps, peripheral edema
   c. The impact on cardiovascular disease is unclear

Prevention of osteoporotic fragility fractures in postmenopausal women

1. Alendronate, etidronate, risedronate
2. strontium ranelate
3. raloxifene (SERM)
4. teriparatide

This guideline assumes that women who receive treatment have an adequate calcium intake and are vitamin D replete. Unless clinicians are confident that women who receive treatment meet these criteria, calcium and vitamin D supplementation should be considered.

Alendronate

1. For vertebral fractures: RR 0.55 (95% CI 0.45 to 0.67)
   a. primary prevention: RR 0.55 (95% CI 0.38 to 0.80) and 2% ARR
   b. secondary prevention: RR 0.55 (95% CI 0.43 to 0.69) and 6% ARR
2. For non-vertebral fractures: RR 0.84 (95% CI 0.74 to 0.94)
   a. secondary prevention: RR 0.77 (95% CI 0.64 to 0.92) and 2% ARR
   b. but not for primary prevention: RR 0.89 (95% CI 0.76 to 1.04).
3. Adverse events:
   a. no statistically significant differences in RCTs.
   b. observational trials: potential risk for upper gastrointestinal injury and, less commonly, osteonecrosis of the jaw.

Strontium

1. Over 3 years with 2 g daily
   a. Vertebral fractures: (RR 0.63, 95% CI 0.56, 0.71)
   b. non-vertebral fractures: (RR 0.86, 95% CI 0.75, 0.98)
2. An increase in BMD was shown at all sites after 2-3 years of treatment
3. Adverse events:
   a. diarrhea.
   b. VTE (RR = 1.42)

Calcitonin

1. increases BMD in postmenopausal women predominantly at the lumbar spine and forearm
2. reduces the risk of vertebral fracture;
3. effect on non-vertebral fracture remains uncertain.

Fluoride

1. Increases BMD at lumbar spine, but it does not reduce of vertebral fractures.
2. In increasing the dose of fluoride, one increases the risk of non-vertebral fracture and gastrointestinal side effects without any effect on the vertebral fracture rate.