Menopause and HRT

Dr. J. Hollett-Caines

Menopause

- Literally means "the end of monthly cycles"
- Defined as ≥ 1 year of no menses (amenorrhea) in women who are:
  - not lactating,
  - not pregnant,
  - and have an intact uterus

Menopause

- mean age in N. America: 51-52 yrs
  - range 45-55 yrs
- age of menopause is genetically predetermined

Who goes into menopause earlier?

- Smokers
- undernourished women
- vegetarians
- women living at high altitudes

Menopause is a time of relative estrogen deprivation

- prior to menopause, **estradiol** is the main source of Estrogen
- most estrogen in postmenopausal women is **estrone**, a weak estrogen
- estrone is derived from peripheral conversion of **androstenedione**

Menopausal Symptoms

- Vasomotor Instability
- Urogenital Atrophy - Sexuality and Libido
- Cardiovascular Disease
- Mood Changes
- Memory and Cognition
- Bone Health – Osteoporosis
- Weight Gain
- Hair Changes

Vasomotor Instability

- **Hot Flashes:**
- Sudden onset of redness of skin of the head/neck/chest
- accompanied by a feeling of intense body heat
- and concluded by profuse perspiration

Hot Flashes

- Duration: seconds to minutes
- Frequency: rare to frequent
- more frequent at **night** or in **stress**
- lasts 1-2 yrs and occurs in perimenopause as well as menopause

Lifestyle Modifications for Hot Flashes

- Reduce core body temperature
- Regular exercise
- Weight management
- Smoking cessation
- Avoidance of triggers (hot drinks, alcohol)

Treatment of Hot Flashes

- **Estrogen - only proven therapy**
- Progesterone - clonidine
- Naloxone - Methyldopa
- SSRI's/SNRI's - Ditropan
- Gabapentin - Bellergal
- herbal remedies
  - soy, isoflavones, evening primrose oil, ginseng, dong quai, black cohosh, flaxseed

Urogenital Atrophy

- **Urinary Atrophy:**
- Urge Incontinence
- Stress Incontinence
- Frequent Urination
- Dysuria (painful urination)
- Nocturia (wake from sleep to urinate)
- Frequent UTI's

Vaginal Atrophy

- Vaginal dryness
- Vaginal burning/itching
- Dyspareunia

Sexuality and Libido

- 2 main sexual changes in the aging female:
- decrease rate of production and volume of vaginal lubrication
- some loss of vaginal elasticity

Sexuality and Libido

- thus during intercourse, feel dryness and burning
- post-coital may have spotting and soreness
- possible treatments: vaginal estrogen (tablets,cream,rings), lubricants

Urogenital Atrophy

Treatment options: non-hormonal and hormonal:

- Water based lubricants (e.g. Astroglide)
- Vaginal moisturizer (e.g. Replens)
- Local Hormonal Therapy (can be used in addition to systemic HT)

Urogenital Atrophy

- Local hormonal therapy available in:
  - Estrogen creams
  - Estrogen rings
  - Estrogen tablets
- Progestin co-therapy is not required for endometrial protection in women receiving vaginal estrogen therapy in appropriate doses

Vaginal Estrogen Preparations

CEE Cream/ Estragyn
CEE 0.5 gm (1/4 of an applicator) for 2 weeks, then twice weekly

Ring
Intravaginal sustained-release
Change every 3 months

Tablet
Estradiol vaginal tablets (10ug)
One vaginal tablet everyday for 2 weeks, then twice weekly

Modified from SOGC Guidelines: Canadian Consensus on Menopause, JOGC, No 171, February 2006.

Stress Incontinence

- Women should be encouraged to try nonsurgical options:
  - Weight loss
  - Weighted vaginal cones
  - Functional electrical stimulation
  - Pelvic floor physiotherapy
  - Pessaries
  - Fluid restriction and decrease caffeinated drinks

Estrogen therapy may be recommended before corrective surgery

Urge Incontinence

- Bladder drills
- Antimuscarinic therapy (Ditropan)
- Fluid restriction and decrease caffeinated drinks

Sexuality and Libido

- Some women experience a decrease or loss of libido in menopause
- Can lead to personal distress
- Endogenous testosterone levels have not been clearly linked to sexual function in postmenopausal women – don't measure

Sexuality and Libido

- Women with decreased libido and no other identifiable cause may be candidates for Testosterone therapy
- Transdermal route are preferable
  - patch or gels/creams
- Dose of 300 mcg/d
- Women need to be aware there is a lack of long-term safety data on testosterone supplementation

CVD

- CVD is the **leading cause of death and disability** among women in Canada
  - 4 of every 10 deaths
  - 3.8 million days in hospital
- most CVD results from **atherosclerosis** in major vessels - risk factors:
  - HTN, abdominal obesity, diabetes, smoking, psychosocial stress

CVD

- During reproductive years, women have lower risk of CVD than men
- this advantage is lost with increasing age

CVD

- Best thing you can do to decrease your risk of CVD is **LIFESTYLE MODIFICATION**
  - Balanced, heart healthy diet
    - Replace saturated fats with mono/polyunsaturated fats, increase omega-3 fatty acids
  - Moderate exercise
  - Maintain healthy body weight
  - Avoid smoking
  - Limited consumption of alcohol
  - Treatment of known risk factors
    - HTN, DM, hypercholesterolemia

Mood, Memory and Cognition

- Estrogen alone may be offered as an effective treatment for depressive disorders in **perimenopausal** women and may augment response to SSRI's
- Estrogen is not currently recommended for reducing the onset or slowing the progression of dementia in postmenopausal women
- However limited data suggests that early use of HRT in menopause may be associated with diminished risk of later dementia

Mood, Memory and Cognition

- Hot flashes may adversely affect mood, memory and cognition by causing sleep disturbances

Osteoporosis

- Bone is an active organ
- Have bone **resorption** and bone **formation**
- aging and **estrogen deprivation** leads to increased **bone resorption**

Skeleton consists of 2 bone types:

- **Cortical bone** (80%):
  - is the bone of the peripheral skeleton
    - Lose 5% per yr in menopause
- **Trabeculated bone**
  - spinal column, pelvis, and proximal femur
    - Lose 1.5% per yr in menopause
- Fracture risk depends on bone mass at menopause and rate of bone loss following menopause

Definitions of Bone Loss:

- Osteopenia:
  - low bone mass, no fractures yet
- Osteoporosis:
  - low bone mass with fractures

Risk Factors for Osteoporosis:

- Age
- Race (asians>white>black)
- Lack of Estrogen
- Body Weight (lean > obese)
- Drugs (heparin, steroids, thyroxine, anticonvulsants)
- Diseases
  - renal, hepatic, hyperthyroid/parathyroid
- Lifestyle
  - Smoker, sedentary, low Ca/VitD, XS caffeine and Etoh

Signs or Symptoms of Osteoporosis:

- Back pain
- Decrease height
- Decrease mobility
- Fractures (vertebrae, humerus, femur, ribs)

Treatment Osteoporosis:

- Estrogen
- Selective estrogen receptor modulators (SERMS)
- Calcium supplementation
- Vitamin D supplementation
- Ca: 1500 mg/day
- Vit D: 800 IU/day
- Bisphosphonates
- Calicitonin
- Fluoride
- Tibolone
- Thiazides
- Lifestyle modifications

Weight Gain

- Increased abdominal fat (male distribution)

Hair Changes

- Loss or thinning of hair on top of head
- Gain hair on face/chin and neck

History of HRT

Year	Event
1928	Estrogen patch for menopause symptoms
1942	Premarin 1.25 mg approved by FDA
2002	WHI E+P trial: Risks of CEE+MPA outweigh benefits over 5.2 years
2004	WHI E-alone trial: no overall benefit over 6.8 years
After 2004	Subgroup analysis of WHI demonstrate favorable results for early postmenopausal women (< than 10 years of menopause)

History of HRT

- In 1990 in the USA, 30 million women were taking menopausal hormone medication
- In 1992, Premarin was the number 1 most prescribed drug in the USA
- Based on data from long term observational studies, it was felt that hormone therapy reduced cardiovascular disease and provided quality of life benefits
- In order to prove the benefits of menopausal hormone therapy, the WHI trial was designed

History

- The Women's Health Initiative (WHI) was conceived as a double blind RCT, designed to prove as a primary endpoint that hormone therapy reduced cardiovascular morbidity and mortality
- The hormone trial had two studies: the estrogen-plus-progestin study of women with a uterus and the estrogen-alone study of women without a uterus
- Premarin and Provera were the drugs chosen

History

- The WHI was launched in 1991 and involved 161,808 postmenopausal women
- To reduce expenses and get answers faster they accepted menopausal women up to age 79

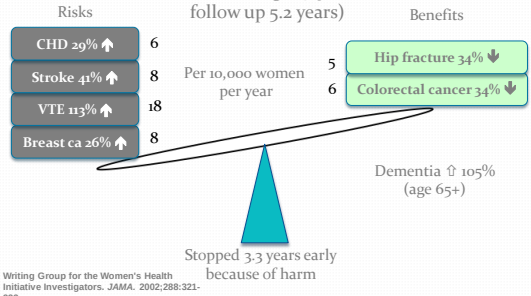
History

Women recruited to the WHI were:

- Older (average age 63, range 50-79, 65% over age 60, 21% over age 70)
- Overweight (average BMI 28.5, 35% over 30)
- Unhealthy (35% on treatment for high BP, 13% on treatment for high cholesterol, 7.5% with previous MI, angina, CABG, stroke or PE)

WHI E+P Trial, 2002

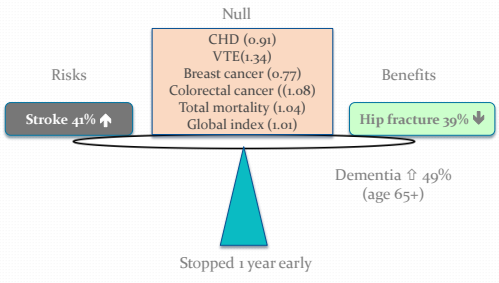
(N=16,608; mean age 63 years; mean follow up 5.2 years)



Writing Group for the Women's Health Initiative Investigators. *JAMA*. 2002;288:321-333.

WHI E-Alone Trial, 2004

(N=10,739; mean age 63.6 years; mean follow up 6.8 years)



Women's Health Initiative Steering Committee. *JAMA*. 2004;291:1701-12.

Vasomotor Symptoms

- HT is the most efficacious therapy for VMS
- Cochrane database review showed[1]
  - 75% reduction in frequency for any HT
  - Significant reduction in hot flash severity
  - Combination of E+P slightly more effective than E alone
- Progestin alone has also demonstrated some efficacy[2]

1. MacLennan, et al. Cochrane Database Syst Rev 2004;2(4):CD002978.
2. SOGC Guidelines: Canadian Consensus on Menopause, *JOGC*, No 171, February 2006.

Vasomotor Symptoms

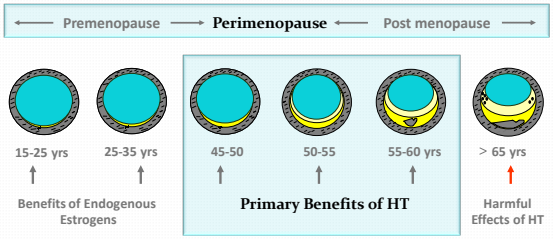
- Health care providers should offer ET or HRT as the most effective therapy for hot flashes
  - Lowest dose possible for the shortest duration
  - Patients should be made aware of the risks of HRT
- There is limited evidence of benefit for most complementary and alternative approaches to the management of hot flashes

Cardiovascular Disease

- Conflicting Data:
  - WHI showed an increase in CV disease and deaths in women on hormone therapy, where other studies have shown a reduction in cardiovascular morbidity and mortality
  - When WHI results were stratified according to age, younger women have shown a reduction in cardiovascular morbidity and mortality
- This may be explained by the concept of a critical therapeutic window for the intervention to show a benefit

Window of Opportunity for Hormone Therapy

There is increasing evidence that ET/HT initiated during the perimenopausal/early postmenopausal period inhibits the progression of atherosclerosis



Adapted from Clarkson, T., NAMS Annual Meeting Oct 2006

Potential Cardiovascular Effects of Hormone Therapy

Oral Estrogen

- Enhances endothelial function in younger post-menopausal women but not in older women with established vascular disease
- Increases serum triglycerides
- Can cause prothrombotic effects such as reduction in serum fibrinogen, Factor VII and AT3
- Increases hepatic synthesis of vascular inflammatory markers such as C-reactive protein

Rosano et al. Ann N Y Acad Sci 2006; 1092:341
Brosnan et al. Thromb Haemost 2007; 97:558

Potential Cardiovascular Effects of Hormone Therapy

The addition of Synthetic progestins may negate the beneficial effect of estrogen on endothelial function and increases production of IL-6 which in combination with increased C-reactive protein sets up an inflammatory pathway

This effect is not seen with natural progesterone

Rosano et al. Ann N Y Acad Sci 2006; 1092:341

Critical Therapeutic Window

- timing of exposure to estrogen therapy is an important factor in determining subsequent cardiovascular risk
- older age at therapy initiation likely associated with more subclinical atherosclerosis
- complex atherosclerotic lesions may be more susceptible to the prothrombotic, proinflammatory effects of estrogen
- There is now ample evidence that HRT has no role in reducing future risks of CVD events in women with established CAD (HERS study)

Hormone Therapy - CV Risks

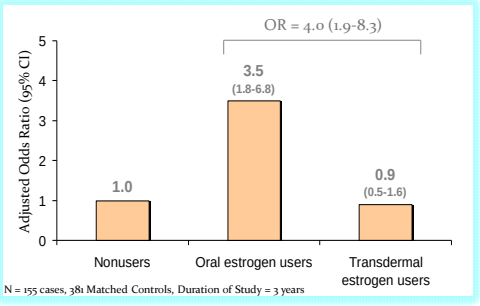
- It would appear that **age at initiation** of hormone therapy is a critical feature in provision of cardiovascular protection
- **Choice of progestogen** also appears to have an effect *
- **Synthetic progestins**, norethisterone and medroxyprogesterone, have been associated with metabolic and vascular side effects in both experimental and human controlled studies
- Thought to **suppress the vasodilating** effects of estrogen
- These effects appear to be **avoidable** with the use of **micronized progesterone**

*de Lignieres B, Clin Ther. 1999 Jan;21(1):41-60

CVD

- HOWEVER, ET or HRT should not be initiated or continued for the sole purpose of preventing CVD
- Instead, recommend lifestyle changes and correction of pre-existing risk factors:
  - DM, HTN, Obesity, smoking, stress

Hormone Therapy - Risk of VTE: Results of the ESTHER Trial (2003)



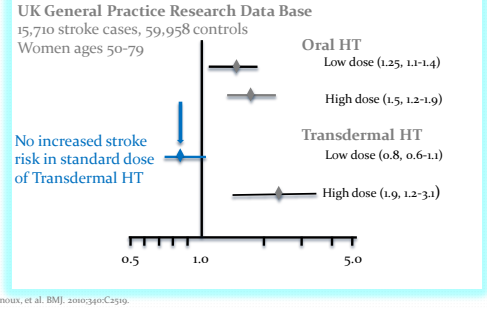
N = 155 cases, 381 Matched Controls, Duration of Study = 3 years

Estrogen and Thromboembolism Risk: Scarabin P-Y, et al. Lancet. 2003;362:428-432

Hormone Therapy Risks - VTE

- The route of estrogen administration as well as the type of progestogen are important determinants of VTE risk among postmenopausal women who use HT
- It would appear that the **single biggest contributor** to VTE risk was **mode of administration**, with transdermal application of estrogen showing no increased risk
- Choice of progestogen was important as well, with micronized progesterone use with transdermal estrogen showing a reduced RR of VTE

Hormone Therapy – Stroke Risk Oral vs. Transdermal Administration



Renoux, et al. BMJ. 2010;340:C2519.

Hormone Therapy Risks - Stroke

- Again, it would appear that route of administration plays an important part in stroke risk
- The use of a transdermal preparation at doses of 50 micrograms per day or less show no increased stroke risk*

*Renoux, et al. BMJ. 2010;340:C2519.

HRT and Breast Cancer

- The risk of breast cancer associated with HRT is the risk of greatest concern to women and their physicians
- WHI (EPT): 8 additional cases of breast cancer per 10,000 hormone users per year. The E only arm did not show an increased risk of breast ca
- WHI detected no increase in the risk of breast cancer with HRT for < 5 years
- Risk returns to normal shortly after discontinuation of HRT

Risk Factors for Breast Cancer

Factor	Baseline Breast Ca/1,000 Women	Additional Breast Ca/1,000 Women	Total Breast Ca/1,000 Women
No HT use (baseline)	45	0	45
5 years HT use	45	2	47
10 years HT use	45	6	51
15 years HT use)	45	12	57
Alcohol (2 drinks/d)	45	27	72
Lack of regular exercise	45	27	72
Late menopause by 10y	45	13	58
BMI index (10 kg/m² ⇧)	45	14	59
Weight gain (≥20 kg)	45	45	90
Late childbearing and reduced breast feeding	45	45	90

SOGC Guidelines 2006

Breast Cancer and HRT

- Women choosing HRT for relief of hot flashes need to understand that short-term hormone use is unlikely to alter their personal risk for breast cancer
- Rates of continuation of HRT for > 5 years after hysterectomy
  - 3% for women using EPT
  - 10% for women using E only

Family History of Breast Cancer

- With breast cancer diagnosed **after age 50**
  - Single 1st degree family member = 12% risk
    - Slight increase in risk over general population
  - 2 first degree relatives = 24%
- With breast cancer diagnosed **before age 50**
  - Single 1st degree family member = 24%
  - 2 first degree relatives = 48%
    - 1st degree relative = mother, sister, daughter

Family History of Breast Cancer and HRT

- Use of hormones was NOT associated with an increase in risk of breast cancer
- Was associated with a reduction in overall mortality from breast cancer
- Genetic influence overshadows any small effect of hormonal exposure

Breast Cancer Survivors and HRT

- HABITS trial in Scandinavia (RCT of 442 women)
- Increased risk of new breast cancer event in women who took HRT for hot flashes (39 cases vs 17 cases over 4 years)

Hormone Therapy Risks - Breast Cancer

- It would appear that choice of progesterone is the critical factor in the increased risk of breast cancer in users of hormone therapy (WHI, E3N, Million Women Study)
- Use of a micronized progesterone with estrogen appears to stabilize the risk of breast cancer, especially with duration of use of five years or less

Conclusions:

- **Lifestyle modification** is very important in mid-life
- Menopausal hormone therapy is beneficial for hot flashes
- The **ideal candidate** in whom to initiate HT would be a woman aged **50-59**, who is less than 10 years from menopause

Conclusions:

- **Timing** and **route** of administration, as well as **choice of progesterone**, are important factors to consider when prescribing hormone therapy
- Use of a transdermal estrogen and micronized progesterone appear to be safer
- Do not recommend HRT/ET for prevention of CVD, memory/cognition, or bone health

Conclusions:

- HRT should be offered to a woman with premature ovarian failure (< age 40 yrs) or early menopause and is recommended to continue until the age of natural menopause (age 51-52)