Menopause and HRT

Henry G. Burger
Hudson Institute of Medical Research
Melbourne, Australia
Disclosures: Henry Burger

Sources of Funding

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**World Health Organisation**
Chairmanship of scientific group on research on the menopause
Mortality rates in women

Source, ABS, Causes of Death, Australia, 1996 Cat. No. 3303.60
Global Consensus-Menopausal Hormone Therapy (MHT) (1)

- MHT most effective treatment-benefits outweigh risks partic. <age 60, < 10 yrs since mp.
- Effective and appropriate for osteoporosis-related fracture prevention in same groups.
- Standard dose E-alone may decrease CHD and all-cause mortality in same groups; combined MHT neutral.
- Local low-dose E for vaginal symptoms.
- E appropriate post-hysterectomy, P required if uterus intact.
- Option of MHT is an individual decision.
Global Consensus-Menopausal Hormone Therapy (2)

- VTE and ischaemic stroke risk increase with oral MHT but absolute risk rare <60. Observational studies point to lower risk with transdermal therapy.
- Breast cancer risk > 50 a complex issue-primarily associated with P addition. Risk is small, decreases after treatment stopped.
- Dose and duration of MHT should be individualised.
- In POI, systemic MHT recommended until average age of natural menopause.
- Use of custom-compounded bio-identical HT not recommended.
- Current safety data do not support use of MHT in breast cancer survivors.
The WHI Hormone Therapy Trials (1)

- Two RCTs were done:
  - combined, continuous daily therapy (CCT) with conjugated equine estrogen (CEE, 0.625mg) and medroxyprogesterone acetate (2.5mg) in women with an intact uterus.
  - CEE (0.625mg) alone in hysterectomised women

- Both were chronic disease prevention trials in older, postmenopausal women of average age 63 years, 70% overweight or obese, 50% hypertensive, 50% past or current smokers.
The WHI Hormone Therapy Trials (2)

- Two main questions were posed:
  - Does a standard regimen of the hormones usually used to treat menopausal symptoms reduce cardiovascular risk?
  - Does the treatment increase breast cancer risk significantly?
Figure 3. Absolute Risks of Health Outcomes by 10-Year Age Groups in the Women’s Health Initiative Hormone Therapy Trials During the Intervention Phase

None of the age interactions were statistically significant (at the $P < .05$ level), except for colorectal cancer, all-cause mortality, myocardial infarction, and the global index in the CEE alone trial (details appear in Figure 5). CEE indicates conjugated equine estrogens; MPA, medroxyprogesterone acetate.
Invasive Breast Cancer
Participants with No Prior Hormone Use

Unweighted HR = 1.09
(95% CI, 0.86-1.40)
Weighted Z = -1.70
Weighted P = 0.090

Invasive Breast Cancer
Participants with Any Prior Hormone Use

Unweighted HR = 1.87
(95% CI, 1.19-2.92)
Weighted Z = -3.15
Weighted P = 0.002
Invasive breast cancer

Overall\textsuperscript{a}

Postintervention\textsuperscript{b}

Cumulative Hazard

0.05

0.04

0.03

0.02

0.01

0

1

2

3

4

5

6

7

8

9

10

11

12

13

Years

No. at risk

CEE  

5310  5166  5007  4840  4261  3620  1696

Placebo  

5429  5280  5106  4915  4301  3678  1771

4697  3635  3438

4756  3670  3459

Figure Legend:

Vertical dotted lines represent quintiles of duration of intended intervention and follow-up in the study population (elapsed time from randomization until the end of the intervention on February 29, 2004). CEE indicates conjugated equine estrogens.\textsuperscript{a}Includes events from randomization to August 14, 2009.\textsuperscript{b}Includes events from March 1, 2004, to August 14, 2009.
Breast Cancer – Conclusions from WHI

• Combined HT may increase breast cancer risk after 5 – 7 years in non-prior users of hormone therapy. There was no evidence of a risk increase before that. However, time since menopause at which treatment is initiated may be important, with risk increasing earlier for initiation close to menopause.

• Estrogen alone in hysterectomised women may decrease breast cancer risk in the first five years, but ultimately an increase in risk may occur.
Table 3. Relative risks for invasive breast cancer by type of HRT and duration of exposure, compared with HRT never-use

<table>
<thead>
<tr>
<th>HRT type and duration of exposure (years)</th>
<th>Cases/FY^a</th>
<th>Relative risk^b (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>766/244,632</td>
<td>1.00 (0.83–1.22)</td>
</tr>
<tr>
<td>Estrogen alone</td>
<td>246/72547</td>
<td>1.19 (1.02–1.65)</td>
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<tr>
<td>&lt;2</td>
<td>246/72547</td>
<td>1.26 (0.83–1.89)</td>
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<tr>
<td>[2–4[</td>
<td>185,705</td>
<td>1.13 (0.79–1.81)</td>
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<tr>
<td>[4–6[</td>
<td>143,372</td>
<td>1.50 (0.88–2.56)</td>
</tr>
<tr>
<td>6+</td>
<td>130,301</td>
<td>1.31 (0.76–2.28)</td>
</tr>
<tr>
<td>p for trend</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>Estrogen + progesterone</td>
<td>129/40,537</td>
<td>1.00 (0.83–1.22)</td>
</tr>
<tr>
<td>&lt;2</td>
<td>188,697</td>
<td>0.71 (0.44–1.14)</td>
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<tr>
<td>[2–4[</td>
<td>33,116,447</td>
<td>0.95 (0.67–1.36)</td>
</tr>
<tr>
<td>[4–6[</td>
<td>307,619</td>
<td>1.26 (0.87–1.82)</td>
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<tr>
<td>6+</td>
<td>43,10,111</td>
<td>1.22 (0.89–1.67)</td>
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<tr>
<td>p for trend</td>
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<tr>
<td>Estrogen + medrogestone</td>
<td>108/31,045</td>
<td>1.16 (0.94–1.43)</td>
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<tr>
<td>&lt;2</td>
<td>166,923</td>
<td>0.84 (0.51–1.38)</td>
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<td>[2–4[</td>
<td>288,697</td>
<td>1.16 (0.79–1.71)</td>
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<tr>
<td>[4–6[</td>
<td>215,590</td>
<td>1.28 (0.83–1.99)</td>
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<tr>
<td>6+</td>
<td>357,876</td>
<td>1.32 (0.93–1.86)</td>
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<tr>
<td>p for trend</td>
<td>0.16</td>
<td></td>
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<tr>
<td>Estrogen + progestagens</td>
<td>527/104,243</td>
<td>1.69 (1.50–1.91)</td>
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<tr>
<td>&lt;2</td>
<td>86/22,792</td>
<td>1.36 (1.07–1.72)</td>
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<tr>
<td>[2–4[</td>
<td>134,50,189</td>
<td>1.59 (1.30–1.94)</td>
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<tr>
<td>[4–6[</td>
<td>106,19,942</td>
<td>1.79 (1.44–2.23)</td>
</tr>
<tr>
<td>6+</td>
<td>156,23,817</td>
<td>1.95 (1.62–2.35)</td>
</tr>
<tr>
<td>p for trend</td>
<td>0.01</td>
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Observational data from
Breast Cancer – Overall Conclusions from RCT and Observational Studies

- No overall statement re risk of HRT is possible:

- For Australian women in the early postmenopause, absolute increase in risk may vary from 0 – 12 additional cases per 1000 women per five years

- Some forms of combined HRT may increase risk especially in lean women treated with Norethisterone or MPA

- Risk may increase after three years in those at highest risk

- Risk assessment is part of the overall consideration of the benefits and risks of hormone therapy
Cardiovascular Disease
Conclusions

• The WHI trial results for CVD were consistent with experimental observations in primates (cynomolgus) that HT is protective against atherosclerosis when initiated immediately after oophorectomy, but is no longer protective after a two year delay.

• In WHI (CCT) HR for CVD risk was:
  0.89 for women <10 years postmenopausal
  1.71 for those >20 years postmenopausal

• In the E only arm, cardioprotection noted in those aged 50-59.

• Recent further analysis (Rossouw et al JAMA 2007) stated that in the 50-59 year age group, “low or no absolute excess risks of CHD, stroke, total mortality…..due to hormone therapy”. There were 10 fewer deaths per 10,000 person years.

• “The low or absent excess risk of CHD in women with <10 years since menopause may be somewhat reassuring….”.

• “Offer some reassurance that hormones remain a reasonable option for the short-term treatment of menopausal symptoms”.
HRT and cardiovascular events in recently postmenopausal women: randomised trial

Schierbeck LL et al., BMJ 2012: 345 e6409 (November)

- Open label, randomised controlled trial in 1006 healthy women, aged 45-58, recently postmenopausal or perimenopausal, 502 on HRT, 504 untreated controls.

- Treatment was with oral triphasic oestradiol (E2) and norethisterone acetate (NA) (2mg E2 12 days, added NA 1mg for 10 days, 1 mg E2 6 days) n=407, or E2 2 mg daily for hysterectomised women N=95.

- At inclusion, average age 50, 7 months postmenopausal.

- Primary outcome was a composite of death, hospital admission for heart failure and myocardial infarction.
HRT and cardiovascular events (2)

- After 10 years of randomised follow-up, primary outcome occurred in
  - 18 on HRT
  - 33 controls  HR 0.48 (0.26-0.87 p=0.015)
- Mortality 15 vs 26
- Breast cancer 10 treated, 17 control
- Conclusion: HRT associated with a significantly reduced risk of mortality, heart failure or myocardial infarction, without any apparent increase in risk of cancer, VTE or stroke.
The timing hypothesis and hormone replacement therapy: A paradigm shift in the primary prevention of coronary heart disease in women: PART 1 Comparison of therapeutic efficacy: PART 2 Comparative risks


- Outcome data from intervention trials in men not generalisable to women.
- Standard primary prevention therapies of statins and aspirin reduce CHD in men, not in women under primary prevention conditions.
- HRT significantly reduces CHD and mortality in primary prevention in women less than 60, or less than 10 years since menopause.
- Majority of risks are rare (HRT <1 in 1000) or infrequent (<1 per 100 treated women).
- HRT can be safely used to reduce CHD and total mortality in women <60, less than 10 years since menopause.
Indications for HRT

Menopausal symptoms

- Relieved by HRT
  - Hot flushes
  - Sweating
  - Sleep disturbance

- May be improved by HRT
  - Fatigue
  - Irritability
  - Nervousness
  - Depressed mood

- Progestogens can potentiate or oppose the action of oestrogens

Urogenital atrophy

- Atrophic changes in the urogenital tract and their consequences (e.g. vaginal dryness, dyspareunia, urinary frequency and urgency)
- Topical low-dose products are the treatment of choice if only local symptoms present

Prevention and treatment of postmenopausal osteoporosis
Suggested Management Schedules (1)

- Indications for treatment:
  - Moderate to severe symptoms interfering with QOL
  - Fracture risk reduction in women <60 years of age

- Before entering or within 1-2 years of final menses:
  - Low dose OC if perimenopausal
  - Sequential therapy

- More than 1-2 years postmenopause:
  - Combined continuous therapy
  - Tibolone
Suggested Management Schedules (2)

- Sequential therapy:
  - Estradiol 0.5 – 1mg orally or
    25-37.5µg transdermally, or
    0.5mg gel or:
  - Conjugated equine estrogens: 0.3-0.45 mg orally

PLUS Norethisterone 0.7mg orally for 12 days per month
or 140/250 mcg transdermally for 14 days (sequi patch)
or MPA 10mg
or Progesterone 200mg (currently requires authorised prescriber)
or Dydrogesterone 10mg
Suggested Management Schedules (3)

- For combined continuous therapy:
  Estradiol or CEE - as per sequential

PLUS
  - Drospirenone 2mg daily
  - or
  - Progesterone 100mg (currently requires authorised prescriber)
  - or
  - Dydrogesterone 5mg
  - or
  - Norethisterone 0.35mg orally
    (or 140/250 mcg transdermally continuous patch)
  - or
  - MPA 2.5 – 5mg
  - or
  - LNG IUD (Mirena)

OR
  - Tibolone 1.25 – 2.5mg daily
Characteristics of transdermal estradiol

- Resembles delivery of ovarian estradiol into the circulation
- Availability of wide range of dosage forms with estradiol-only patches
- No intestinal metabolism and no hepatic first-pass effect
- Thus relatively small conversion to estrone sulphate, hence reduced pool of circulating estrogen in comparison with orally administered estradiol
- No increase in hepatic synthesis of clotting factors, binding proteins
- Hence absent or greatly decreased risk of VTE, lack of effect on SHBG and bio-available testosterone
- Can monitor absorption by measuring plasma estradiol
- Little if any effect on plasma lipids
- Can cause local skin reactions
When should transdermal (or parenteral) estradiol be prescribed?

- When oral estrogen causes nausea, g-i discomfort
- In cigarette smokers
- Disorders associated with malabsorption eg coeliac disease, IBS, g-i surgery, patients on PPIs
- In patients with elevated triglycerides, liver disease
- Increased risk of CVD eg history of CVD, obesity, diabetes, age>60 when initiating treatment
- Increased risk of VTE including past history of DVT, family history of spontaneous VTE, sedentary occupation, known coagulation factor abnormality
TIBOLONE – An alternative to hormone therapy

- Synthetic steroid – precursor molecule metabolised in a tissue selective fashion
- Estrogenic effects on bone, vagina and menopausal symptoms, but not on the breast
- Progestogenic effects on the endometrium
- Androgenic effects
- Single oral daily dose-2.5 mg.

Efficacy of Tibolone (1)

- As effective as EPT/ET for symptom management
- Reverses vaginal atrophy and improves vaginal dryness, dyspareunia and urinary symptoms
- Affects sexual well-being positively
- One RCT in FSD – marginally superior to transdermal E2 and NETA
- May positively affect mood, QOL
- At a dose of 1.25 mg prevents bone loss and reduces fracture risk in women > 60 over 3 years (LIFT – NEJM 2008: 359:697-708)
Efficacy of Tibolone (2)

- Causes less breast tenderness and mastalgia than EPT
- Does not increase mammographic density
- Effect on breast cancer uncertain – in LIFT at 1.25 mg dose, in women > 60, over 3 years RH = 0.32, effect similar to first three years of WHI CCT trial
- In UK General Practice Research Data Base RR=0.87
- No significant endometrial stimulation in short term studies
- Cardiovascular effects unclear – in LIFT, NS
- Stroke risk increased in women > 60, especially > 70
- No increase in VTE risk
- Well tolerated
Tibolone After Breast Cancer

• LIBERATE is a RCT comparing Tibolone with placebo in women treated for breast cancer (in contrast to women without breast cancer)

• The recurrence rate over 3 years was - 15.2% in Tibolone treated women.
  - 10.5% in placebo treated women

• Overall treated breast cancer remains a contraindication to Tibolone use
HRT After Breast Cancer

- Treated BrCa generally regarded as a contra-indication
- 3 randomised studies have given conflicting results:
  - LIBERATE evaluating Tibolone showed increased recurrence rate predominantly in AI treated women
  - HABITS showed increased recurrence rate, low numbers, low use of tamoxifen, use of combined continuous therapy
  - STOCKHOLM showed no increase in recurrence rate, low numbers, higher frequency of tamoxifen, long cycle intermittent progestin use.
- Meta-analysis of 7 observational studies with controls showed
  - RR for recurrence 0.5
  - RR for cancer-related mortality 0.3 (Batur et al Maturitas, 2006)

- THE MAJOR ISSUE IS QOL IN AN INFORMED PATIENT
Choice of Treatment

- For young risk-free woman: oral or transdermal E (+or-P) or tibolone
- For women >60 requiring symptomatic treatment: low dose transdermal E
- For woman with increased VTE risk: transdermal E-type of P may be important
- For woman with CVD risk factors eg obesity, diabetes, lipid abn (incl inc’d TGs), clinical CHD: transdermal E
- For women who require bone protection and are risk-free: oral or transdermal E or tibolone
- For women with low libido: tibolone or testo with or without transdermal E
- For women with treated BrCa: low dose transdermal E + progesterone (intermittent) if possible
Testosterone

- Use in Australia is ‘off label’

- Main available female-specific product is 1% testo cream from Lawley in Perth

- Can be tried in women with unexplained fatigue, distressing loss of libido and low free testo levels. Response rate is 50-60%

- Should be considered in young women (<45) partic. with hypopituitarism, adrenal failure and/or ovarian failure requiring HRT.
Suggested Management Schedules (4)

- Treatment reviewed annually by halving dose or discontinuing and assessing need for continued therapy
- No arbitrary time limit re duration of therapy
Risks / benefits of HRT (oral estrogen) – 50-59yrs

<table>
<thead>
<tr>
<th></th>
<th>Risks</th>
<th>Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women ages 50-59</td>
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Santen et al JCEM July 2010, 95: S7-66
Risks / benefits of HRT – 50-59yrs

Santen et al JCEM July 2010, 95: S7-66
Take home messages (1)

- HRT is the first-line and most effective treatment for menopausal symptoms. Choice of preparation and route of administration must be individualised. Annual review is recommended.
- Quality of life is a central issue.
- HRT does not increase and may decrease CHD risk in healthy women when initiated near the time of menopause. Early harm not seen in this group.
- Stroke risk in this group low.
- VTE risk doubled with oral but not transdermal therapy (in observational studies). Background prevalence low in peri- and early post-menopausal women except in those who are obese or who have a thrombophilia.
Take home messages (2)

• Level I evidence indicates that, up to 5 years, combined HRT does not significantly increase breast cancer risk in first time users. However time from FMP of treatment initiation may be important. Estrogen alone and Tibolone may not increase risk. The type of progestin used in combined therapy may be important.

• HRT is a cost effective first-line treatment for osteoporotic fracture risk reduction in 50-59 year old post-menopausal women.

• Transdermal estradiol plus progesterone may be the optimal choice.
Suggested recommendations (1)

• Benefits of HRT include
  – Symptom relief
  – Improved QOL
  – Reduction in risk of osteoporotic fracture
  – Reduction in risk of colorectal cancer with some types

• Risks of HRT (some types)
  – Venous thromboembolism
  – Breast cancer after prolonged therapy
Suggested recommendations (2)

- Breast cancer risk of similar magnitude to
  - Early menarche
  - Late menopause
  - Late first pregnancy
  - Obesity
  - Moderate alcohol intake

- Management of menopausal symptoms must be individualised