Menopause Management

Symptoms and management

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This presentation is intended for NZ Healthcare Professionals Only. Please consult your doctor regarding menopause treatment management.
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The menopausal transition

- A process which takes about a decade
- Early signs include
  - shortening of the menstrual cycle by 2–3 days, detectable at about age 38–40\textsuperscript{1,2}
  - infertility – with associated oocyte aging, increased incidence of luteal insufficiency and anovulation\textsuperscript{3}
    abnormal basal temperature in 30–50% of cycles after age 40\textsuperscript{4,5}
- Menopause is marked by exhaustion of the ovarian supply of oocytes\textsuperscript{6,7}, numbers declining steeply from age 37–38

\textsuperscript{1}Lenton 1984; \textsuperscript{2}Klein 1996; \textsuperscript{3}Treloar 1970; \textsuperscript{4}Döring 1963; \textsuperscript{5}Vollmann 1977; \textsuperscript{6}Baker 1963; \textsuperscript{7}Richardson 1987
Ovarian follicle numbers

Richardson et al. JCEM 1987

Primordial follicles/ovary

Age (years)

0 10 20 30 40 50 60

Primordial follicles/ovary

0 1 10 100 1000 10000 100000

Richardson et al. JCEM 1987

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Estrogen production at menopause
Age of menopause

- Age range of 45–55 years world-wide. Anything from 42yrs onwards is regarded as normal.
- The final period occurs at 50–52 years in white women from industrialized countries.
- It is earlier in women from less well developed areas of the world.
Menopause Symptoms

- Sx of the menopause transition may begin 5-10 yrs before periods stop and reflect the swings in hormone levels
- Sx related to estrogen deficiency continue on average for 4-8 years.
- 20% of women will have long-term sx
- Different ethnic groups may have different experiences of menopause
- A surgical or chemo-induced menopause is not the same as a natural menopause
  - The sx are worse and last for longer
Symptoms

- Symptoms clearly related to estrogen deficiency include:
  - Vasomotor symptoms and related sleep disturbance
  - Vaginal or genital dryness
  - Recurrent UTIs
  - Joint pain or stiffness
  - Generalized aches and pains
  - Sexual dysfunction
  - Mood disturbance
  - Cognitive changes – NOT improved with MHT

Barnabei et al., 2005 Obstet Gynecol, Welton et al., 2008 BMJ
KEEPS Study, NAMS 2012, ELITE study 2016

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Persistence of menopausal symptoms

Mean duration of vasomotor symptoms is 8 years.
- 50% still symptomatic at 4 years
- 10% still symptomatic at 10 years

I DON'T HAVE HOT FLASHES...

I HAVE SHORT, PRIVATE VACATIONS IN TROPICAL-LIKE CONDITIONS!
Why do we have hot flushes?

No hot flushes

<table>
<thead>
<tr>
<th>Sweat</th>
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<tbody>
<tr>
<td>Thermoneutral zone</td>
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<tr>
<td>Shiver</td>
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</tbody>
</table>

Hot flushes

<table>
<thead>
<tr>
<th>Hot flush</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thermoneutral zone</td>
</tr>
<tr>
<td>Chills</td>
</tr>
</tbody>
</table>

Hot flushes are more than just a nuisance!

24-Apr-17

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Vasomotor symptoms

- Flushes are not benign symptoms
- Significant adverse changes in cerebral blood flow are seen during a hot flush
- Changes in cognitive function are seen during a hot flush
- The presence of severe flushes acts as a predictor of future CV disease and dementia

Resnick et al., 1998; Maki et al, 2000
Menopause transition

Flushes
Night sweats
Joint and muscle aches
Sleep disturbance
Mood and cognitive change
Vaginal dryness
Sexual dysfunction

Genito-urinary problems
Osteoporosis
Increased CAD risk

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Management of menopause

Alternative and prescription therapies.
What works?
First step in management

• Listen to the woman
  • What worries her the most?
  • What are her concerns about treatment options?
• Assess the impact of her symptoms
• Assess risk of cardiovascular disease and fractures
  • Cholesterol
  • Blood pressure
  • Glucose
  • Bone density.

24-Apr-17

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Updated Recommendations

2016 IMS Recommendations on women’s midlife health and menopause hormone therapy

R. J. Baber, N. Panay & A. Fenton the IMS Writing Group

To cite this article: R. J. Baber, N. Panay & A. Fenton the IMS Writing Group (2016) 2016 IMS Recommendations on women’s midlife health and menopause hormone therapy, Climacteric, 19:2, 109-150, DOI: 10.3109/13697137.2015.1129166
To link to this article: http://dx.doi.org/10.3109/13697137.2015.1129166

Menopause: diagnosis and management
NICE guideline [NG23] Published date: November 2015
“A lost decade”

Menopause Management — Getting Clinical Care Back on Track
JoAnn E. Manson, M.D., Dr.P.H., and Andrew M. Kaunitz, M.D.
NEJM 374 (9); 2016

“Reluctance to treat menopausal symptoms has derailed and fragmented the clinical care of midlife women, creating a large and unnecessary burden of suffering. “
Menopause Hormone Therapy

• Estrogen alone (oral or transdermal)
• Estrogen + progestogen (oral or IUS)

Benefits:
  • Reduces sx
  • Reduces risk of colon cancer
  • Reduces fracture risk
  • Reduces risk of CAD
  • Reduces all cause mortality
  • Estrogen alone reduces breast cancer risk

Risks:
  • Age related – CVA/VTE
  • Progestogen related – breast cancer

• Estrogen + SERM (TSEC)

Please review Data Sheet for Information on approved indications for individual treatment options

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Women’s Health Initiative and Coronary Heart Disease

A: Intervention phase. B: Cumulative 13yr f/up

Manson et al., JAMA 2013;310(13)

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Risk of death or admission for HF or MI

DOPS study, Schierbeck et al., BMJ 2012;345

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Change in LDL cholesterol

mg/dl

0 1 3 4

-7 -6 -5 -4 -3 -2 -1 0 1 2 3

0 CEE
t E2
Placebo

KEEP Study – NAMS 2012

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Change in Insulin Resistance

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KEEPs Study – NAMS 2012
Type II Diabetes Incidence

E+P WHI

RR decrease in E+P arm 0.77 (0.64-0.93)

Adjusted for age, baseline BMI and change in BMI

Similar reduction seen in E only trial, HERS study and E3N study

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Systolic Blood Pressure

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Diastolic Blood Pressure

mmHg

0 0.5 1 2 3 4
Years

-2.5 -2 -1.5 -1 -0.5 0

Placebo
t E2 o CEE

KEEP Study – NAMS 2012

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### CAD and HRT

**Analysis 4.2. Comparison 4 Subgroup analysis of timing hypothesis (<10 years versus >10 years since menopause), Outcome 2 Coronary heart disease (death from cardiovascular causes and non-fatal myocardial infarction).**

**view:** Hormone therapy for preventing cardiovascular disease in post-menopausal women

**comparison:** 4 Subgroup analysis of timing hypothesis (<10 years versus >10 years since menopause)

**outcome:** 2 Coronary heart disease (death from cardiovascular causes and non-fatal myocardial infarction)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>HT (n/N)</th>
<th>Control (n/N)</th>
<th>Risk Ratio M-H,Random,95% CI</th>
<th>Weight</th>
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<tbody>
<tr>
<td>Hormone therapy commenced &lt;10 years after menopause</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>COPPS 2012</td>
<td>6/502</td>
<td>22/504</td>
<td>0.27 [ 0.11, 0.67]</td>
<td>25.2 %</td>
</tr>
<tr>
<td>HRT II 1979</td>
<td>1/84</td>
<td>3/84</td>
<td>0.33 [ 0.04, 3.14]</td>
<td>6.4 %</td>
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<tr>
<td>WHI I 2002</td>
<td>31/2782</td>
<td>35/2712</td>
<td>0.86 [ 0.53, 1.40]</td>
<td>41.5 %</td>
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<tr>
<td>WHI II 2004</td>
<td>8/826</td>
<td>16/817</td>
<td>0.49 [ 0.21, 1.15]</td>
<td>26.8 %</td>
</tr>
<tr>
<td><strong>btotal (95% CI)</strong></td>
<td><strong>4194</strong></td>
<td><strong>4117</strong></td>
<td><strong>0.52 [ 0.29, 0.96]</strong></td>
<td>100.0 %</td>
</tr>
</tbody>
</table>
### Analysis 4.1. Comparison 4 Subgroup analysis of timing hypothesis (<10 years versus >10 years since menopause), Outcome 1 Death (all-causes).

**Review:** Hormone therapy for preventing cardiovascular disease in post-menopausal women

**Comparison:** 4 Subgroup analysis of timing hypothesis (<10 years versus >10 years since menopause)

**Outcome:** 1 Death (all-causes)

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<td></td>
<td></td>
</tr>
<tr>
<td>DOPS 2012</td>
<td>15/502</td>
<td>26/504</td>
<td>23.2 %</td>
<td>0.58 [0.31, 1.08]</td>
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<tr>
<td>EPHT 2006</td>
<td>1/404</td>
<td>1/373</td>
<td>1.2 %</td>
<td>0.92 [0.06, 14.71]</td>
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<tr>
<td>ERT II 1979</td>
<td>3/84</td>
<td>7/84</td>
<td>5.2 %</td>
<td>0.43 [0.11, 1.60]</td>
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<tr>
<td>WHI I 2002</td>
<td>39/2782</td>
<td>46/2712</td>
<td>50.3 %</td>
<td>0.83 [0.54, 1.26]</td>
<td></td>
</tr>
<tr>
<td>WHI II 2004</td>
<td>14/826</td>
<td>21/817</td>
<td>20.1 %</td>
<td>0.66 [0.34, 1.29]</td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>4598</strong></td>
<td><strong>4490</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.70 [0.52, 0.95]</strong></td>
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*Boardman et al., 2015 Cochrane Library*
Stroke

• The risk of stroke is age–related.
• There is no significant increase in stroke risk in women using MHT under 60yrs or within 10 years of LMP unless there are other risk factors for stroke.
• Transdermal therapy is preferred in any woman with risk factors for stroke or VTE eg. obesity, hypertension, migraine, diabetes
Early atherogenesis

Beneficial effects of HRT

\[\uparrow\text{Vasodilation}\]
\[\uparrow\text{Nitric oxide}\]
\[\downarrow\text{Endothelin}\]
\[\uparrow\text{Cox-2}\]

\[\downarrow\text{Lesion progression}\]

\[\uparrow\text{Nitric oxide}\]
\[\downarrow\text{Inflammatory cell adhesion}\]

\[\downarrow\text{LDL oxidation/binding}\]

Established atherosclerosis

Altered biology of HRT

\[\downarrow\text{ER expression, function}\]
\[\downarrow\text{Vasodilation}\]
\[\uparrow\text{Inflammatory activation}\]
\[\uparrow\text{Plaque instability}\]

\[\uparrow\text{MMP}\]
\[\uparrow\text{Neovascularization}\]

Source: © 2006 by the American College of Cardiology Foundation
Effect of hormone therapy on fractures

WHI steering Committee JAMA 2002

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Relative risk of colon cancer

BCDDP data, Cancer Epidemiol Biomarkers18(1) 2009
Breast Cancer- WHI Extended Data 2012

Figure 4: Cumulative hazards, adjusted for age and ethnic group, of invasive breast cancer by random allocation in the WHI trials of conjugated equine oestrogen alone and conjugated equine oestrogen plus medroxyprogesterone acetate trials derived from Chlebowski and colleagues. HR=hazard ratio.
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Summary

• Hormone therapy is safe and effective for women within 10 years of menopause

• If older women require ongoing therapy consider the use of transdermal estrogen to avoid the age-related risk of VTE and stroke

• Consider the choice of progestogen with longer term therapy
Menopause Hormone Therapy

IMS governing principles on MHT

- MHT remains the most effective therapy for vasomotor symptoms and urogenital atrophy.

- There are no reasons to place mandatory limitations on the duration of MHT. Data from the WHI trial and other studies support safe use for at least 5 years in healthy women initiating treatment before age 60.

- Whether or not to continue therapy should be decided at the discretion of the well-informed woman and her health professional, dependent upon the specific goals and an objective estimation of ongoing individual benefits and risks.

2016 IMS Recommendations
Baber, Panay, Fenton et al. Climacteric 2016
Menopause Hormone Therapy

• Estrogen alone
  • Hysterectomy
  • Mirena (when used in combination with Estrogens where the uterus is still intact)

• Estrogen plus a progestogen
  • Consider if hysterectomy but severe endometriosis with bowel involvement

• Start with a low dose, adjust after several weeks of therapy
• Aim to largely settle flushes and avoid breast tenderness
• Bleeding may require an adjustment in progestogen dose.

Please review Data Sheet for Information on approved indications for individual treatment options
**Vaginal/vulval symptoms**

- Vaginal lubricants and moisturizers: Sylk, Replens
- Estrogens include: Ovestin cream and pessaries. Vagifem now more difficult to access
- Very low levels of absorption beyond the vagina and bladder
- Generally not contraindicated after gyne or breast cancer
- Topical DHEA and ospemifene

Please review Data Sheet for Information on approved indications for individual treatment options

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Alternatives to HRT

• Exercise
• CAMS: Remifemin(?), St John’s wort, hypnosis, CBT, mindfulness
• SSRI: escitalopram, paroxetine*, venlafaxine
• Gabapentin
• Oxybutynin ER 15mg
• Cetirizine
• Clonidine
• Stellate ganglion blockade

Please review Data Sheet for Information on approved indications for individual treatment options

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Stellate ganglion blockade
Stellate ganglion block
SGB and flushes

Walega et al., Menopause 2014

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SGB and depressive symptoms

FIG. 4. Changes in depressive symptoms for women randomized to SGB or sham control. Data points represent the mean and standard error at each time point. CES-D, Center for Epidemiological Studies—Depression Scale; SGB, stellate ganglion blockade.

Walega et al., Menopause 2014
YouTube Videos

Menopause - Will it Affect my Sex Life?
by International Menopause Society
3 months ago • 231 views
Professor Susan Davis discusses how the onset of menopause may affect your sex life, as well as various treatment options.

Menopause - What are the Symptoms?
by International Menopause Society
1 month ago • 893 views
Professor Susan R. Davis discusses several of the most common menopausal symptoms. View the entire Informational Series: ...

Menopause - What is Menopausal Hormone Therapy (HRT)?
by International Menopause Society
1 month ago • 434 views
Other Resources

- A Practitioner’s Toolkit for Managing the Menopause
  F. M. Jane and S. R. Davis
  CLIMACTERIC 2014;17:564–579

- Menopause. A Primer
  Davis et al.
  Nature Reviews
  Published online 23 April 2015

- MenopauseMatters website
  www.menopausematters.co.uk

- Australasian Menopause Society
  www.menopause.org.au
Menopause: Exploring the evidence

21st Annual Congress
Australasian Menopause Society

Sofitel Sydney Wentworth • 13 – 15 October 2017