Menopause 2014

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Disclosure Statement

- **Speakers bureau, research, travel & educational grant funding in last 5 years:**
  - MSD (was Organon Schering-Plough)
  - Bayer HealthCare
  - Flordis

- **Expert panel and Consultant:**
  - Bayer HealthCare
  - Wyeth Pharmaceuticals (now Pfizer)

- **Director:**
  - Jean Hailes for Women’s Health (a not-for-profit charity)
Menopause: what is it?

- The final menstrual period

"Menopause is easy - after you stop laying eggs, they eat you."
Definitions

• **Menopause**: the final menstrual period
  – Normal, natural event associated with reduced functioning of the ovaries, resulting in lower levels of ovarian hormones (primarily oestrogen).

• **Postmenopause**: 12 months after the final menstrual period and onwards

• **Perimenopause**: from the onset of irregular periods
  – some or all of symptoms such as irregular periods, hot flushes, night sweats or sleep disturbance) to the final menstrual period.
Definitions

• **Early menopause:** final menstrual period between 40-45 years of age

• **Premature menopause:** Final menstrual period prior to 40 years of age
  – Spontaneous or due to chemotherapy, radiotherapy or surgery
A cohort of women in a breast cancer screening program (EPIC), reproductive data were obtained (n = 3,483) and predicted distribution from antral follicle counts in normal fertile women.

### Reproductive cycle

<table>
<thead>
<tr>
<th>Stages:</th>
<th>-5</th>
<th>-4</th>
<th>-3</th>
<th>-2</th>
<th>-1</th>
<th>+1</th>
<th>+2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminology:</td>
<td>Reproductive</td>
<td>Menopausal Transition</td>
<td>Postmenopause</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Terminology:</td>
<td>Early</td>
<td>Peak</td>
<td>Late</td>
<td>Early</td>
<td>Late*</td>
<td>Early*</td>
<td>Late</td>
</tr>
<tr>
<td>Terminology:</td>
<td>Perimenopause</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of Stage:</td>
<td>variable</td>
<td>variable</td>
<td>variable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of Stage:</td>
<td>1 yr</td>
<td>4 yrs</td>
<td>until demise</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menstrual Cycles:</td>
<td>variable to regular</td>
<td>regular</td>
<td>variable cycle length (&gt;7 days different from normal)</td>
<td>≥2 skipped cycles and an interval of amenorrhea (≥60 days)</td>
<td>none</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menstrual Cycles:</td>
<td>Amen x 12 mos</td>
<td>Amen x 12 mos</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocrine:</td>
<td>normal FSH</td>
<td>↑ FSH</td>
<td>↑ FSH</td>
<td>↑ FSH</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hansen et al, Menopause 2012
Endocrinology

(Burger et al, Recent Prog Horm Res. 2002;57:257-75)
LOOP – double ovulation
Duration of the perimenopause

Fig. 8. Duration of menopausal transition.

Treloar AE, Maturitas 1981
Symptoms across the transition

Perimenopause symptoms
- Mood changes
- Sore breasts
- Bloating
- Headaches/migraines
- Periods: irregular in flow & pattern & symptoms

Menopause symptoms
- Hot flushes
- Night sweats
- Sleep disturbances
- Formication
- Joint pains
- Irritability
- Fatigue

Vaginal dryness
Low libido
Urogenital symptoms

80% some symptoms
80% have symptoms for < 5 years
80 % mild to moderate symptoms
Persistence of vasomotor symptoms

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

Midlife stresses

• Psychological
  – Mood changes
  – Depression, initial or recurrence

• Social and family stresses
  – Career peak
  – Aging parents
  – Children: “revolving door”, still at school
  – Changes in partner circumstances
  – Financial
  – Relationship issues
Diagnosing Menopause

• DON’T
  – Check FSH, LH, oestradiol or testosterone levels in a woman with symptoms at the normal age for menopause (over 45 years) because these results are unlikely to change your management. The indications for intervention are clinical.

• DO
  – Take a good history of menopausal symptoms, preferably using a standardised symptom measurement system
  – Record personal medical history and risk factors for breast cancer thromboembolic disease and osteoporosis
  – Take a menstrual history

Because you will offer help to the woman with symptoms and these factors will influence what treatments you advise!
Investigations

Depends on symptoms and issues: e.g.

- **Perimenopause**
  - Bleeding
  - Contraception
  - PMS like symptoms
  - Vasomotor symptoms
  - Mood changes
- **Menopause**
  - Vasomotor symptoms
  - Urogenital atrophic symptoms

Tests

- Depends on history
- Pap smear
- Mammogram
- Regular assessments – FBE, glucose, lipids, TFTs
- Others depending on history
- Hormones FSH/LH/E2 depending on age and sx
- TVUS
Management is about an holistic approach to improving health and wellbeing

“Night sweats and hot flashes are nature’s way of lowering your heating bill so you can save more money for your retirement.”

© 2003 Randy Glasbergen.
www.glasbergen.com
Hormone Replacement Therapy (Menopause Hormone Therapy)

- The appropriate time to initiate HRT is at the onset of symptoms, i.e. near the menopause.

- HRT should be part of an overall strategy including lifestyle recommendations regarding diet, smoking cessation, exercise and safe alcohol consumption to maintain health of peri and post menopausal women.

- The option of MHT is an individual decision in terms of:
  - Quality of life and health priorities as well as
  - Personal risk factors such as age, time since menopause and
  - The risk of venous thromboembolism, stroke, ischemic heart disease and breast cancer.
Global Consensus Statement 2013*

• MHT is the most effective treatment for vasomotor symptoms associated with menopause at any age, but:
  Benefits are more likely to outweigh risks for symptomatic women before the age of 60 years or within 10 years after menopause.

Global Consensus Statement 2013*

- MHT is effective and appropriate for the prevention of osteoporosis-related fractures in at-risk women before age 60 years or within 10 years after menopause.

- Randomized clinical trials and observational data as well as meta-analyses provide evidence that **standard-dose estrogen-alone MHT:**
  - may decrease coronary heart disease and
  - all-cause mortality in women younger than 60 years of age and within 10 years of menopause.

Global Consensus Statement 2013*

• **Oestrogen plus progestogen** MHT in this population show:
  – a similar trend for mortality
  – but in most randomized clinical trials no significant increase or decrease in coronary heart disease has been found.

• **Local low-dose oestrogen therapy** is preferred for women whose symptoms are limited to vaginal dryness or associated discomfort with intercourse.

• **Oestrogen as a single systemic agent** is appropriate in women after hysterectomy but additional progestogen is required in the presence of a uterus.

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* Global Consensus Statement on Menopausal Hormone Therapy de Villiers TJ. *Climacteric* 2013;16:203–204.
Global Consensus Statement 2013*

The dose and duration of MHT should be consistent with treatment goals and safety issues and should be individualised.

• In women with premature ovarian insufficiency, systemic MHT is recommended at least until the average age of the natural menopause.

• The use of custom-compounded bioidentical hormone therapy is not recommended.

• Current safety data do not support the use of MHT in breast cancer survivors.

The risk of breast cancer with MHT

The risk of breast cancer in women over 50 years associated with MHT is a complex issue.

• The increased risk of breast cancer is primarily associated with the addition of a progestogen to estrogen therapy and related to the duration of use.

• The risk of breast cancer attributable to MHT is small and the risk decreases after treatment is stopped.
The risk of breast cancer with HRT use: WHI data

Anderson G et al Maturitas 2006;55:103-115

The Women's Health Initiative Steering Committee
JAMA 2004; 291: 1701-1712
Risk of VTE

- The risk of venous thromboembolism and ischaemic stroke increases with oral MHT but the absolute risk is rare below age 60 years.
- Observational studies point to a lower risk with transdermal therapy.

- MHT-related risk for VTE depends on the route of oestrogen administration…
  - Oral oestrogens increase thrombin generation and induce resistance to activated protein C,
  - Transdermal oestrogens have a minimal effect on hemostasis.

- The combination of oral oestrogen use with VTE risk factors dramatically enhances VTE risk.
Risk of VTE

• Significant differences in VTE risk between MHT preparations are also related to the type of concomitant progestogen.
  – VTE risk is greater in women using medroxyprogesterone acetate (Provera) than in those receiving other progestins,
  – whereas progesterone appears safe.
AMS Guide to Equivalent HRT Doses

### Continous oestrogen & progestagen combinations

<table>
<thead>
<tr>
<th>Product</th>
<th>Presentation</th>
<th>Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premarin®</td>
<td>tablet</td>
<td>1mg oestradiol/1mg mestranol</td>
</tr>
<tr>
<td>Estrace®</td>
<td>tablet</td>
<td>1mg oestradiol/0.2mg medroxyprogesterone acetate</td>
</tr>
<tr>
<td>Estrace cap 50/150</td>
<td>transdermal patch</td>
<td>50mcg 17β oestradiol/150mcg mestranol, once daily weekly application</td>
</tr>
<tr>
<td>Estrostep 50/200</td>
<td>transdermal patch</td>
<td>50mcg 17β oestradiol/200mcg mestranol, once daily weekly application</td>
</tr>
</tbody>
</table>

### Continuous oestrogen & progestagen combinations should be used in 12 months cycle and after 12 months amenorrhoea

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<thead>
<tr>
<th>Product</th>
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<th>Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premarin®</td>
<td>tablet</td>
<td>1mg oestradiol/0.5mg medroxyprogesterone acetate</td>
</tr>
<tr>
<td>Klowine®</td>
<td>tablet</td>
<td>1mg oestradiol/0.5mg medroxyprogesterone acetate</td>
</tr>
<tr>
<td>Livial®, Premarin® (generally suitable for older women or at least 1 year post-menopausal)</td>
<td>tablet</td>
<td>2.5mg oestradiol</td>
</tr>
</tbody>
</table>

### Transdermal implants

<table>
<thead>
<tr>
<th>Oestrogen or progestagen</th>
<th>Amount</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovestin</td>
<td>cream</td>
<td>daily application</td>
</tr>
<tr>
<td>Vapecel</td>
<td>pess</td>
<td>daily application</td>
</tr>
</tbody>
</table>

### Oestrogen only therapy

- Use these if patient has had a hysterectomy or in combination with a progestagen or Mirena if intact utera.

<table>
<thead>
<tr>
<th>Product</th>
<th>Presentation</th>
<th>Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrofem®</td>
<td>tablet</td>
<td>1mg 17β oestradiol</td>
</tr>
<tr>
<td>Premarin®</td>
<td>tablet</td>
<td>1mg oestradiol/0.5mg medroxyprogesterone acetate</td>
</tr>
<tr>
<td>Premarin®</td>
<td>tablet</td>
<td>2mg oestradiol</td>
</tr>
<tr>
<td>Premarin®</td>
<td>transdermal patch</td>
<td>0.2mg conjugated equine oestrogen</td>
</tr>
<tr>
<td>Climara 25, Femtran 25</td>
<td>transdermal patch</td>
<td>25mcg/24 hours 17β oestradiol (weekly application)</td>
</tr>
<tr>
<td>Estrace XT 25 or 37.5</td>
<td>transdermal patch</td>
<td>25 or 37.5mcg/24 hours 17β oestradiol (twice weekly application)</td>
</tr>
<tr>
<td>Estrace XT 25</td>
<td>transdermal patch</td>
<td>5mcg/24 hours 17β oestradiol (twice weekly application)</td>
</tr>
<tr>
<td>Estrace XT 25 (to be discontinued mid 2013)</td>
<td>transdermal patch</td>
<td>25mcg/24 hours 17β oestradiol (twice weekly application)</td>
</tr>
</tbody>
</table>

### Progestagen

- Products which are underlined are Australia only; products in italics are NZ only.
- Products with an * meaning Private/non PBS script.
- Products which are underlined are Australia only; products in italics are NZ only.
- Products with an * meaning Private/non PBS script.

### Sterilization

**Suggested alternative doses for use with the oestrogen preparations above where fixed dose therapy is not suitable**

- Low dose for use with low dose oestrogen

<table>
<thead>
<tr>
<th>Product</th>
<th>Presentation</th>
<th>Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provera (1/2 mg tablet)</td>
<td>tablet</td>
<td>1.25mg medroxyprogesterone acetate</td>
</tr>
<tr>
<td>Provera 2.5 mg tablet*</td>
<td>tablet</td>
<td>2.5mg medroxyprogesterone acetate</td>
</tr>
<tr>
<td>Climara 75 (1/4 of 5mg tablet)</td>
<td>tablet</td>
<td>1.25 mg norethisterone</td>
</tr>
<tr>
<td>Estrace XT 75, Estrace 100</td>
<td>transdermal</td>
<td>2mg medroxyprogesterone (device, 5 years)</td>
</tr>
<tr>
<td>Climara 100, Femtran 99</td>
<td>transdermal</td>
<td>1.25mg norethisterone (implant)</td>
</tr>
<tr>
<td>Estrace XT 100</td>
<td>transdermal</td>
<td>2mg medroxyprogesterone (implant)</td>
</tr>
</tbody>
</table>

### Dose escalation

- Higher dose (for use in cyclic therapy or continuous therapy with high dose oestrogen)

<table>
<thead>
<tr>
<th>Product</th>
<th>Presentation</th>
<th>Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premarin N 1/4 of 5mg tablet</td>
<td>tablet</td>
<td>1.25mg norethisterone</td>
</tr>
<tr>
<td>Provera, Raloxifene</td>
<td>tablet</td>
<td>1mg medroxyprogesterone acetate</td>
</tr>
<tr>
<td>Urogenest (NZ only)</td>
<td>capsule</td>
<td>100mg micronised progesterone</td>
</tr>
</tbody>
</table>

### Continuous oestrogen & progestagen combination

- Low dose progestogen-only contraceptive pills (Miralax® [10mg levonorgestrel], Norinelle® [200mcg norethisterone]) are used by some clinicians in various doses but there is limited data for dosages of these pills required for endometrial protection. 1mg norethisterone was considered the minimum dose (cylical or continuous) for adequate endometrial protection when combined with 2mg 17β oestradiol in the Cochrane Review (Cochrane Database of System Reviews, 2009, 15/07/2008).
Menopause Algorithm

Hormone Replacement Therapy

• Perimenopause & first 2 years postmenopausal
  – Cyclic therapy E+P

• Post menopausal (> 2 – 3 years)
  – Continuous therapy E+P
  – Tibolone

• Post hysterectomy
  – Continuous E
  – Tibolone

• Premature or Early
  – High dose til age 50
Other Therapies

• **Tibolone**
  - Synthetic progestogen derivative
  - Actions of 3 hormones: oestrogen, progesterone, testosterone
  - 3 metabolites
  - Acts along receptor pathway, also enzyme inhibition, lowers SHBG, tissue specific
  - No increase in VTE
  - Less breast stimulation

• **Testosterone**
  - Non-TGA registered
  - Suitable in unexplained fatigue, where libido and low testosterone
  - Appropriate where BSO, patch in Europe for this indication only
Bioidenticals

• Troches, creams compounded by pharmacists
  – Contain estrogens, progesterone, androgens, etc
  – Content based on salivary or blood levels
• Non-TGA approved
• No evidence to support efficacy or safety (ACOG 2005)
• Just another form of HRT
Non- Hormonal Prescriptives

• Clonidine
  – Anti- HT ? Reduces vascular reactivity
  – Used over many years

• SSNIs/SSRIs
  – Antidepressants reduces sx up to 60%
  – On Tamoxifen – not take Paroxetine or Fluoxetine

• Gabapentin
  – Anti epileptic / chronic pain medication

All should work within 4 weeks
Antidepressants for VMS: What works best?

- **Paroxetine** (Paxil) 12.5 mg CR
  - 62% reduction in hot flushes at 6 weeks (Stearns et al 2009)
  - Effective in those who had discontinued HRT (Soares et al 2008)

- **Venlafaxine** (Efexor) 75mg SR
  - 60% reduction in hot flushes at 6 weeks (Loprinzi et al 2000)
  - No objective improvement at 12 weeks (Evans et al 2006)

- **Desvenlafaxine** (Pristiq) 150mg/day
  - 60% reduction in hot flushes at 12 weeks (Archer et al 2009)
Antidepressants for VMS: What works best?

- **Fluoxetine** (Prozac) 20mg
  - 50% reduction in hot flushes at 6 weeks (Loprinzi et al 2002)

- **Escitalopram** 10-20mg
  - 50% reduction in number and severity at 8 weeks (Freeman et al 2011)
Limitations of SSRI/SRNI

• Interaction with tamoxifen
  – Paroxetine and fluoxetine may reduce the active metabolite of tamoxifen (Stearns et al 2004, Jin et al 2005)
  – Increased deaths from breast cancer in tamoxifen users taking paroxetine (Kelly et al BMJ 2010)

• Side effects
  – Dose related
  – Cause up to 20% withdraw from treatment (Stearns 2006)
    • Headache, nausea, anorexia, dry mouth, anxiety/agitation, sleep disturbance and sexual dysfunction
Limitations of SSRI/SRNI

• **Discontinuation syndromes**
  – Primarily with short-acting agents
    • Paroxetine, venlafaxine and desvenlafaxine

• **Lack of efficacy**
  – Around 30% get worse with SSRI/SNRI – unpredictable response (Kirwin et al 2007)
Anticonvulsants for hot flushes

- **Gabapentin** (900 mg/day)
  - 51% reduction in hot flushes at 12 weeks
    (Butt et al 2008, Pandya et al 2005)
  - Equivalent efficacy to estrogen
    (Premarin, 0.625, Reddy et al 2006; 25mcg estradiol patch, Aguirre et al 2010)
  - Pregabalin (75 mg bd) also effective (Loprinzi et al 2010)

- Limitations
  - Cost ($40-100 per month)
  - Side effects in up to 50%
    - Drowsiness, confusion, ataxia
    - Resolved by 4 weeks
      (Butt et al 2008)
OCPs and herbs

• Phytoestrogens - many foods such as soy, legumes and other vegetables.

• Phytoestrogen foods may have a modest effect on vasomotor symptoms.

• Randomised placebo controlled trials commercially isolated phytoestrogens such as isoflavones not demonstrated an effect greater than placebo.
OCPs and herbs

Black cohosh has also not been shown to be significantly better than placebo.

- Most studies are short term and there is no long-term data on the safety and efficacy.
- Now 12/12 study shows significant improvement in Femular (Flordis) daily
- Currently there are no significant effective alternative or complementary therapies or remedies for the menopause and its sequelae.
Menopause 2014

• HRT in healthy women 50-59 years who are symptomatic is low risk.

• Duration of therapy depends on duration of symptoms and an annual risk/benefit analysis.
Menopause 2014

• Complex hormonal changes as periods cease.
• Symptoms may occur
• Quality of life
  – Management strategies
    • Knowledge
    • Self help strategies
    • HRT
    • Non hormonal therapies