Menopause and Mood

Women’s health across the lifespan
GP symposium, Epworth, June 4 2016
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Endocrinologist,
Jean Hailes at Epworth Freemasons & Alfred Hospital

Menopause

- The final menstrual period
- Perimenopause – the time around the final menstrual period
- Average age of FMP 51
- Average onset of perimenopause 47


4/07/2016
Hormones across the menopause transition

One woman's hormones in the months prior to menopause

Menopausal symptoms

• 1 in 3 women have severe psychological symptoms
• 1 in 4 have severe physical symptoms
Menopausal symptoms

- Vasomotor symptoms (hot flushes and night sweats)
- Vaginal dryness
- Sleep disturbance
- Headaches
- Joint pain
- Mood changes

Symptoms can last many years

- For half of women, symptoms vasomotor symptoms last 7 years
- For half of women, vasomotor symptoms persist 4.5 years after the final menstrual period
- Symptoms persist much longer in a substantial number of women
Mood symptoms at menopause

- Women without a history of anxiety are TWICE as likely to develop anxiety in perimenopause and early postmenopause.
  
  Bromberger et al Mopause 2013

- Women are TWO to FOUR times more likely to feel depressed during the menopause transition.
  
  Freeman et al Arch Gen Psych 2006; Bromberger et al Obstet Gynecol Clin North Am 2011

Vasomotor & depressive symptoms

Reference
Fig 1 Profiles of psychological symptoms across midlife and according to age relative to menopause.

Depressive symptom scores by menopausal status

Mean anxiety scores by menopausal status  (lower score = more anxious)
Depressive and anxiety symptoms

- After taking into account body mass index (kg/m²), carer status, marital status, employment, housing security, history of mental illness, smoking, weekly binge drinking and education level,

- Compared to premenopausal women, postmenopausal women ≤ 55:
  - More likely to have depression OR 1.7 (95% CI, 1.1-2.7, p<0.05)
  - Have more anxiety β -1.1 (95% CI, -1.7 - -0.5, p<0.01)

Alcohol, smoking & psychotropic use by menopausal status

Current smoking and alcohol use

- After taking into account body mass index, diagnosis of mental illness, depression, anxiety, and residential location, marital status, education level, employment, housing security

- Compared to premenopausal women, postmenopausal women ≤ 55:
  - More likely to smoke OR 1.6 (95% CI, 1.1-2.5, p<0.05)
  - More likely to drink heavily OR 2.0 (95% CI, 1.3-3.1, p<0.01)
Psychotropic medication use by menopausal status

Menopause and mood
- Mood symptoms improve after the menopause transition but... Freeman et al. JAMA Psychiatry 2014
- This can take years
- Hormone therapy may improve depression during perimenopause Worsley, 2012
- But...
- Many women are intolerant of progestins Andreen, 2010

Hormone therapy
- Estrogen the most effective treatment for hot flushes
- Patches, tablets, gel, pessaries
- Causes endometrial thickening / increased risk of endometrial cancer so women with a uterus must also receive a progestin
- Maybe 30% women negative effects progestin (mood) Andreen, 2010
### HT- risks from WHI

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Estrogen + Progesterin</th>
<th>Estrogen Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer</td>
<td>↑ after 2 years HR 1.24 (95% CI, 1.01-1.53), remains elevated after stopping.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ Early post-intervention HR 0.55 (95% CI, 0.34-0.89)</td>
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<tr>
<td>Stroke</td>
<td>HR 1.37 (1.07-1.76)</td>
<td>HR 1.35 (1.07-1.70)</td>
</tr>
<tr>
<td>DVT</td>
<td>↑ 1.87 (1.37-2.54)</td>
<td>↑ 1.48 (1.08-2.07)</td>
</tr>
<tr>
<td>CHD</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>↔</td>
<td>↔</td>
</tr>
</tbody>
</table>

Chlebowski et al, JAMA Oncol 2015; Mason et al JAMA 2013
Monash Alfred Psychiatry Research Centre

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**Figure Legend:**

Absolute Risks of Health Outcomes by 10-Year Age Groups in the Women's Health Initiative Hormone Therapy Trials During the Intervention Phases of the Trials. Absolute ages 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 estrogen; MPA, medroxyprogesterone acetate.
Change in case number per 1000 women per 5 years of treatment in women aged 50-59

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<th>Estrogen + Progestin</th>
<th>Estrogen only</th>
</tr>
</thead>
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<tr>
<td>All cause mortality</td>
<td>-5.3</td>
<td>-5.0</td>
</tr>
<tr>
<td>CHD</td>
<td>-0.9</td>
<td>-3.8</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>+6.8</td>
<td>-1.5</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>-5</td>
<td>+2</td>
</tr>
<tr>
<td>Stroke</td>
<td>+1.0</td>
<td>+1.2</td>
</tr>
<tr>
<td>Fracture</td>
<td>-0.9</td>
<td>-5.9</td>
</tr>
<tr>
<td>Cholecystitis (all ages)</td>
<td>+9.6</td>
<td>+14.2</td>
</tr>
<tr>
<td>T2DM</td>
<td>-11</td>
<td>-11</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>+1.2</td>
<td>0</td>
</tr>
</tbody>
</table>

Antidepressant use in perimenopausal depression

- Commonly used to treat anxiety, depression, sleep problems, hot flushes
- SNRIs popular (low dose venlafaxine)
- Issues – discontinuity problems, blunting, aggression, problems with tachyphylaxis
- Hypertension w venlafaxine
- ?fracture risk

Menopause and pre-existing mental illness

- Bipolar Disorder
  - More depressive symptoms
  - ?Hormone therapy helpful
- Schizophrenia
  - ?worse mood/QoL ?improvement w age
- Depressive Disorders
  - Recurrence more common
Mood and the menstrual cycle

- Many women notice changes in their illnesses/symptoms with the menstrual cycle
- Changes in mood can also occur
  - Premenstrual Syndrome
  - Premenstrual Dysphoric Disorder
  - Premenstrual Exacerbations of Depression/Anxiety
- PMS often worsens in the 40s as women approach menopause

The menstrual cycle

For a 28 day cycle:
- Day One – first day of bleeding
- Day 14 – ovulation
- Follicular phase: Day 1 – Day 14
- Luteal Phase: Day 15-28
- Premenstrual: 5 days (or more!!) before bleeding e.g. Day 23-28

Premenstrual syndrome

- Symptoms in the 1-2 weeks before a period that get better after a period
- Around 80% of women notice some symptoms premenstrually – normal!
Premenstrual syndrome

More intrusive symptoms
- Physical
- Emotional & behavioural
Bloating

Anxiety

Cravings
Low mood

Common symptoms of PMS

Fatigue
Irritability
Bloating
Anxiety/tension
Breast tenderness
Mood lability
Depression
Food cravings
Acne

Increased appetite
Oversensitivity
Swelling
Expressed anger
Crying easily
Feeling of isolation
Headache
Forgetfulness
Gastrointestinal symptoms
Poor concentration
Hot flashes
Heart palpitations
Dizziness

Premenstrual dysphoric disorder

- PMDD diagnosis focuses on mood

- 5-10% women reproductive age
PMDD diagnosis

Five of:
- depression, irritability, anxiety, affect lability
- decreased interest, difficulty concentrating, fatigue, feeling out of control, insomnia, change in appetite, breast tenderness, breast swelling
- interfere with usual activities

PMDD Diagnosis: CYCLICITY

- Symptoms occur in the luteal phase, remit in the first few days of cycle.
- Symptom free in follicular phase.
- Diagnosis requires a 2 month daily DIARY

Tests

- No diagnostic tests
- Look for:
  - Other illnesses – thyroid
  - Menopause transition
  - Other mood disorder
  - Current medications
**cause**

- Hormonal fluctuations in the menstrual cycle
- Normal hormone levels / Different brain response
- Progesterone metabolite → Allopregnanolone
- Inflammatory markers in luteal phase (IL-4, IL-10, IFN-γ; affective symptoms correlate w IL-2, physical symptoms w IL-4)

**Physiological ALLO concentrations**

- 100nM/L
- 5nM/L
- Pregnancy (0-40 weeks)
- Menstrual cycle

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ALLO in PMDD? A paradoxical response

ALLOpregnanolone concentration

IRRITABILITY SCORE

Low
High
Low
Luteal
High

Neuropsychopharmacology

Improvement in symptoms by avoiding luteal rise in allopregnanolone by blocking 5 alpha reductase

Treatment - lifestyle

- Diet? low salt? low GI? more carbs
- Maintain weight
- Sensible alcohol use
- Exercise - throughout cycle
- Avoid smoking
- Stress reduction
- Planning
Treatment - over the counter

- Calcium
- Vitex agnus castus (Chasteberry)
- Other herbs: St John’s Wort

Treatment - medication

- Oral contraceptive pill use continuously (take sugar pills every three months)
- Antidepressants (SSRIs) help brain to better respond to hormonal fluctuations
- Other

The oral contraceptive pill

- Estrogen + progestin
- High discontinuation rate due to mood side effects
- Progestins cause worse mood in some women
Progestin in the OCP & anxiety disorders

Depression scores by oestrogen dose

Choosing an OCP

• It’s difficult!
• Mood SEs with OCP I like:
  – Zoely
  – Qlaira
  – Valette
• & I avoid Yaz/Yasmin
Mood symptoms at menopause

• Is it my hormones?
• Usually it's a bit of everything
• Often need a combination of therapies:
  – Lifestyle measures
  – Psychological therapies
  – Hormone therapy
  – Antidepressants