Menopause & PMS
Endocrinology and Management

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Hypothalamo-pituitary ovarian axis

Feedback hormones

Steroids

Inhibin

Gonadotropins: - LH, FSH

Ovary
Hormone levels over a normal menstrual cycle
Testosterone levels over the menstrual cycle

[Sinha-Hakim et al, JCEM (83) 1998]
Menstrual patterns in reproductive aging
Within CNS, estrogen acts as a neuroprotective agent

- Genomic (delayed)
  - mediated by the activation of estrogen receptors and gene transcription
- Non-genomic (rapid)
Estrogen, progesterone and neurotransmitters

- Estrogen regulates the activity and synthesis of serotonin and acetylcholine
- It interacts with noradrenaline and dopamine
- Estrogen generally lifts mood
- Progesterone, via a metabolite, alters the GABA system and enhances MAO activity. The latter decreases noradrenaline, dopamine and serotonin
- Progestogens may lower mood and enhance sedation
Mood and the menstrual cycle

- Individual vulnerability to normal hormone changes lead to:
  - PMS/PMDD
  - Post-natal depression
  - Menopause related mood changes, anxiety and psychosis

- It is often the change in hormone levels rather than the absolute level that is the problem

- It may be the same women who present with recurrent hormone-related mood issues at different stages of their reproductive lives.
Hormone levels over a normal menstrual cycle
Androgens and mood

- Excess androgen has been associated with:
  - low mood
  - anxiety
  - increased risks of PMS and eating disorders, particularly bulimia

- Mental health issues not tightly linked to the presence of sx
Androgen excess

Not all women with androgen excess have obvious signs.
Polycystic ovary syndrome

- Affects 5-10% of women regardless of ethnicity
- A genetically determined metabolic disorder
- Insulin resistance triggers weight gain and excess androgen production
- Women may present with irregular periods, acne, hirsutism, alopecia and/or weight gain.
- They may have no sx at all
- Effects on fertility and CV health
Menstrual Mood disorders
Menstrual mood disorders

- PMS/PMDD becomes more common with age, particularly after 35yrs of age
- It is triggered by hormone swings mid-cycle and pre-period
- A cascade of changes in neurotransmitters and other hormones (androgens, mineralocorticoids) then occur and cause both physical and psychological sx.
- If PMS presents at before 30yrs there is often an underlying hormone disorder driving this, particularly polycystic ovary syndrome
Premenstrual Syndrome

- 40% of reproductive age women report sx of PMS
- 3-8% have sx that meet the criteria for PMDD.
- Women with PMDD have a 50-75% lifetime incidence of psychiatric disorders
- Mutations in the estrogen receptor have been detected in women with PMDD
- The average woman has usually seen multiple doctors over a period of years before the diagnosis is made
- Sx begin after ovulation and resolve early in the menstrual cycle.
- There is always a clear window without sx during the later follicular phase of the cycle
- The pattern is consistent over 2-3 cycles

Huo et al., Biol Psychiatry. 2007;62(8):925-33
Menstrual mood disorders

- Modulating hormone swings has a significant impact on menstrual mood disorders

- Treatment options include:
  - Diet/lifestyle
  - Calcium/magnesium
    - Low ionized calcium in women with PMDD
  - Yaz
    - Anti-androgen and anti-mineralocorticoid
  - Spironolactone
    - Anti-androgen and anti-mineralocorticoid
  - Cyproterone
    - Anti-androgen and anti-gonadotrophic
  - SSRIs
    - Rapid onset of action suggests effect may be largely due to hormone modulation
  - LrH analogues to create a medically-induced menopause + estrogen/progestogen
A study of hormone modulation
Cyproterone acetate acts as an anti-androgen and anti-gonadotropin.

- It suppresses hormone swings and ovulation to a greater degree than the OCP.
- It is combined with estradiol to maintain stable estrogen levels.

Fenton et al., 2015 submitted
Design

- Prospective study of women starting cyproterone acetate for treatment resistant menstrual disorders at Christchurch Women’s Hospital and Southern Cross Hospital, Christchurch.

- Women with active liver disease, a history of VTE or those lacking capacity to give informed consent were excluded.

- Cyproterone 50mg daily + estradiol 2mg/50ug were prescribed after a comprehensive history and examination and baseline blood tests.

- The women were reviewed after 3mths of therapy. Clinical examination and blood tests were repeated. Doses were adjusted as required.

- All women gave informed consent.

- The data is shown for 200 consecutive women seen between 2008 and 2013.
Medical Diagnoses

Number of women

- PCOS
- PMS/PMDD
- Migraine
- Pelvic Pain
- Perimenopause
- Cyclical vomiting
Average age

Age (yrs)

PCOS

PMS/PMDD

Migraine

Pelvic pain

Perimenopause

Cyclical vomiting
Menopause
Definitions

- **Menopause**
  - The final menstrual period

- **Perimenopause**
  - The transition through the early stages of menopause when periods begin to change in length and sx may begin to occur

- **Postmenopause**
  - 12 months after the final menstrual period
Definitions

- Early menopause
  - Last period between 40 and 45 yrs

- Premature menopause
  - Last period before 40 yrs
  - May be spontaneous or induced by surgery or cancer treatment
## STRAW Classification

<table>
<thead>
<tr>
<th>Stage</th>
<th>Terminology</th>
<th>Menstrual Cycle</th>
<th>Duration</th>
<th>PRINCIPAL CRITERIA</th>
<th>SUPPORTIVE CRITERIA</th>
<th>DESCRIPTIVE CHARACTERISTICS</th>
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</thead>
<tbody>
<tr>
<td>-5</td>
<td>Reproductive</td>
<td>Variable to regular</td>
<td>variable</td>
<td>Variable Length Persistent ≥7 day difference in length of consecutive cycles</td>
<td>FSH Low</td>
<td>Vasomotor symptoms Likely</td>
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<td>-4</td>
<td>Reproductive</td>
<td>Regular</td>
<td>1-3 years</td>
<td>Variable Length</td>
<td>AMH Variable Low</td>
<td>Vasomotor symptoms Most Likely</td>
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<tr>
<td>-3b</td>
<td>Reproductive</td>
<td>Regular</td>
<td>2 years (1+1)</td>
<td>Persistent ≥7 day difference in length of consecutive cycles</td>
<td>Inhibin B Low</td>
<td>Vasomotor symptoms Most Likely</td>
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<td>Reproductive</td>
<td>Regular</td>
<td>3-6 years</td>
<td>Interval of amenorrhea of ≥60 days</td>
<td>Antral Follicle Count Low</td>
<td>Vasomotor symptoms Likely</td>
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<tr>
<td>-2</td>
<td>Menopausal Transition</td>
<td>Subtle changes in flow/length</td>
<td>Remaining lifespan</td>
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<td>Perimenopause</td>
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<tr>
<td>+2</td>
<td>Postmenopause</td>
<td>Late</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Blood draw on cycle days 2-5 = elevated

**Approximate expected level based on assays using current international pituitary standard**
Diagnosis of menopause

- There is no blood test that tells you where a women is in menopause or how much longer the transition will take
- Just listen to the patient!
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\(^1,2\)
  - infertility – with associated oocyte aging, increased incidence of luteal insufficiency and anovulation\(^3\)
    abnormal basal temperature in 30–50% of cycles after age 40\(^4,5\)

- Menopause is marked by exhaustion of the ovarian supply of oocytes\(^6,7\), numbers declining steeply from age 37–38

\(^1\)Lenton 1984; \(^2\)Klein 1996; \(^3\)Treloar 1970; \(^4\)Dòring 1963; \(^5\)Vollmann 1977; \(^6\)Baker 1963; \(^7\)Richardson 1987
Estrogen production at menopause
Androgens in the menopausal transition

- In normal women, there is a 50% decrease in circulating concentrations of testosterone and dehydroepiandrostosterone sulphate (DHEAS) from age 20 to age 45\(^1,2\)
- There is little if any decline in testosterone during the transition\(^2,3\)
- DHEAS levels continue to fall with age, with no specific association with the transition
- The medical ‘myth’ that menopause is associated with an acute drop in androgens does not appear to be tenable any longer

\(^1\)Zumoff 1995, \(^2\)Davison 2005; \(^3\)Burger 2000
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.
Factors involved in earlier age of menopause:
- oophorectomy, e.g. for endometriosis, cancer
- chemotherapy, e.g. cyclophosphamide
- ovarian irradiation
- hysterectomy (up to 4 years advancement)
- familial and genetic factors (e.g. ER-α polymorphism, twinning)
- cigarette smoking – by about 2 years

Factors involved in later age of menopause:
- possibly later age at menarche, oral contraceptive use, longer menstrual cycle length, polycystic ovary syndrome and parity
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.
The Seven Dwarves of Menopause

Itchy, Bitchy, Sweaty, Sleepy, Bloated, Forgetful & Psycho
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

_Barnabei et al., 2005 Obstet Gynecol, Welton et al., 2008 BMJ KEEPS Study, NAMS 2012_
I DON'T HAVE HOT FLASHES...

I HAVE SHORT, PRIVATE VACATIONS IN TROPICAL-LIKE CONDITIONS!
Prevalence of vasomotor symptoms

Regular menstrual bleeding

Pre/perimenopause (months since last menstrual bleeding)

Postmenopause (years since last menstrual bleeding)

Estradiol levels: absolute vs change

Severity

Absence

Moderate/severe

Oldenhave, et al. AJOG 1993;168:773
Body temperatures during hot flushes

Adapted from Molnar. *J Appl Physiol* 1975;38:499–503
Menopause and mood

- 1 in 3 women will experience psychological sx
- Perceived stress and anxiety are both associated with depression in midlife women
- The rates of women experiencing their first episode of depression during the peri-menopausal years have been found to be anywhere from 2 to 14 times higher than in the premenopausal years
- Debate continues as to the role of estrogen deficiency vs sleep deprivation in altering mood and cognitive function.
- It is probably a mixture of both.

Worsley et al., Maturitas 2014 77(2):111-7
Gibbs et al., Women Health Issues 2013 23(5):301
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
*Coronary heart disease, heart failure, stroke, or intermittent claudication.

Management of menopause
Menopausal 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
Menopausal Hormone Therapy

- Clearly the most effective treatment for symptom control
- There is no consistent formula that works for every woman.
- Adjustment of doses is critical
- Studies show mood improves in 68-80% of women
Surgical Menopause

• Women with a surgical menopause may need much higher doses and longer therapy with estrogen to settle sx

• The risks of menopause before age 45yrs are substantial and hormone therapy should be used unless there are very good reasons not to. HRT should be continued until the normal age of menopause
Alternatives to HRT

- Exercise
- CAMS: Remifemin, St John’s wort, acupuncture, hypnosis, CBT, mindfulness
- SSRI: escitalopram, paroxetine*, venlafaxine
- Gabapentin
- Cetirizine
- Clonidine
- Stellate ganglion blockade
Hypnosis

**FIG. 2.** Change in weekly composite hot flash scores.

Elkins *et al.*, Menopause 2013
Escitalopram

Change from baseline in quality of life, comparing hormone therapy with escitalopram.

Soares et al., Menopause 2006
FIG. 2. A: Mean Insomnia Severity Index from baseline to week 8 by treatment assignment. B: Mean Pittsburgh Sleep Quality Index from baseline to week 8 by treatment assignment. Vertical bars represent SE.
Stellate ganglion blockade
YouTube Videos

Menopause - Is Menopausal Hormone Therapy (HRT) Safe?
by International Menopause Society
1 month ago • 305 views
Professor Rod Baber discusses the safety of menopausal hormone therapy (HRT).
View the entire Informational Series: ...

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
Professor Susan Davis discusses the basics of menopausal hormone therapy (HRT). View the entire Informational Series: ...
Take home messages

- Hormones have significant effects on neurotransmitters and mood
- Individual women may have increased vulnerability to normal hormone changes over their reproductive lives
- Understanding the pathophysiology opens up a wide range of treatment options
Menopause - Mind over Matter

19th Congress of the Australasian Menopause Society
Friday 25 to Sunday 27 September, 2015, Hotel QT Canberra, Australia