Endocrinology, Menstrual cycle, Menopause and Management

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Female Menstrual Cycle

- Relevance to psychiatry?
- Missing history, missing link?
- Another arm to therapy?
- Management?
- Reducing silo medicine
Should Psychiatrists be prescribing oestrogen therapy to their female patients?

BJPsych 2013
The Obstetrician-Gynecologist’s role in detecting, Preventing and treating Depression

Obstet Gynecol 2017
Hormone Roller Coaster
Hypothalamic-pituitary ovarian axis

Feedback hormones

Hypothalamus

GnRH

Pituitary

Gonadotropins: - LH, FSH

Steroids

Inhibin

Ovary
Hormone levels over a normal menstrual cycle
Within CNS, estrogen acts as a neuroprotective agent

- Genomic (delayed)
  - mediated by the activation of estrogen receptors and gene transcription
- Non-genomic (rapid)
Rats/Mice

- Long term oestradiol changes social behaviour and gene expression in the brains of rats (Garcia 2017)
- Estradiol treatment in rats provides lasting enhancement of memory and brain oestrogen receptor activity (Pollard 2018)
- Rhesus monkeys – oestrogen increases dendritic numbers in hippocampus and pre-frontal cortex (Hara 2015)
Humans

- Estrogen HRT may preserve neurologic function and reduce the risk of dementia if started early in menopause (cohort data)

- Keeps study (RCT) 75 women (mean age 53 years) MRI assessments at Mayo clinic at 18, 36, 48 months during treatment and 3 years after treatment.

- Cortical volumes declined in both groups but volume of the dorsolateral prefrontal cortex was preserved more in E2 group at 3 years (Kantarci 2018)
Estrogen, progesterone and neurotransmitters

- *Estrogen* lifts mood, regulates activity and synthesis of serotonin and acetylcholine
- Interacts with noradrenaline and dopamine
- *Progesterone*, alters the GABA system and enhances MAO activity which decreases noradrenaline, dopamine and serotonin
- Progestogens may lower mood and enhance sedation
Mood and the menstrual cycle

- Individual reactions to hormone cycle changes:
  - PMS/PMDD
  - Post-natal depression
  - Menopause related mood changes, anxiety and psychosis
  - Migraine

- The change in hormone levels is the problem
- Recurrent at different stages of reproductive lives.
Hormonal Soup
History

- Is the mood disorder cyclical?
- Before periods
- Ask about post natal depression
- Previous episodes of depression
- LMP?
- Previously stable
- Night sweats?
Menstrual Mood disorders
Sally (45 years of age)

- PMS symptoms are getting worse- become crippling
- Gets very angry for the second half of the cycle
- Negative self talk ,memory shot, affecting work ,Dark places
- Has 2 young children- not safe for 2 days of the month
- Period comes- “lights get switched back on”
- Feels better when she is pregnant, felt awful on the depo provera
Menstrual mood disorders

- PMS/PMDD increase with age, particularly after 35yrs
- Hormone swings mid-cycle and pre-period
- A cascade of changes in neurotransmitters and hormones occurs leading to physical and psychological sx.
- PMS before 30yrs there is often an underlying hormone disorder, particularly polycystic ovary syndrome
PMS symptoms

- Mood swings,
- Irritability, depression, anxiety,
- Bloating, fluid retention, breast tenderness,
- Sugar cravings,
- Headaches and poor sleep

Tell them they are not going mad and we can alleviate symptoms although it may take time
Premenstrual Syndrome

- 40% of reproductive age women report sx of PMS
- 3-8% meet the criteria for PMDD.
- **PMDD**: 50-75% lifetime incidence of psychiatric disorders
- Mutations in the estrogen receptor have been detected in women with PMDD
- Sx begin after ovulation and resolve early in the 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
Hormone levels over a normal menstrual cycle
Reducing hormone swings

- Diet/lifestyle/exercise
- Calcium/magnesium
- Yaz - Anti-androgen, anti-mineralocorticoid
- Spironolactone
- Cyproterone - Anti-androgen and anti-gonadotrophic (FSH, LH)
- SSRIs
  - Rapid onset of action
- Medically-induced menopause + estrogen/progestogen (GnRH agonists-zoladex)
Use of oestrogens

• Patch in luteal phase
• HRT (half a Trisequens)
• Add back progesterone if uterus present
• Take a good Hx and follow up
Polycystic ovary syndrome

- Genetically determined metabolic disorder
- 5-10% of women regardless of ethnicity
- Insulin resistance triggers weight gain and excess androgen production
- Irregular periods, acne, hirsutism, alopecia and/or weight gain.
- They may have no sx at all
- Effects on fertility and CV health
Menopause
The Menopause – What Is IT!

Simply means stopping of periods

- It represents a significant endocrine (hormone) change in a women.
- Average age is 51.
Definitions

- Menopause
  - The final menstrual period

- Perimenopause
  - The transition when periods begin to change in length and sx may begin to occur

- Postmenopausal
  - 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
Diagnosis of menopause

- Information is power - women need reassurance this is normal
- Need to take a good history – timing and symptoms
- 80% of women have symptoms
- Blood tests are not helpful
The menopausal transition

- Takes about a decade

- Early signs
  - menstrual cycle shortens by 2–3 days, detectable at about age 38–40\textsuperscript{1,2}
  - infertility – oocyte aging, increased incidence of anovulation\textsuperscript{3} basal temperature up in 30–50\% of cycles after 40 years age\textsuperscript{4,5}

\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
Determinants of the age of menopause

- oophorectomy, e.g. for endometriosis, cancer
- chemotherapy, e.g. cyclophosphamide
- ovarian irradiation
- hysterectomy (up to 4 years earlier)
- familial and genetic factors (e.g. ER-α polymorphism, twinning)
- cigarette smoking – by about 2 years
Symptoms clearly related to estrogen deficiency

- Vasomotor symptoms
- Vaginal or genital dryness
- Recurrent UTIs
- Joint pain or stiffness
- Generalized aches and pains
- Sexual dysfunction
- Mood disturbance
- Palpitations

Barnabei et al., 2005 Obstet Gynecol, Welton et al., 2008 BMJ
KEEPS Study, NAMS 2012
Menopause Symptoms

- Who gets symptoms?
- 5-10 yrs before periods stop and reflect the swings in hormone levels
- 20% of women will have long-term sx
- Different ethnic groups may have different experiences of menopause
- May be last straw- Grief reactions, co-morbidities (including mental health), other life stresses
- A surgical or chemo-induced menopause have worse symptoms for longer.
These symptoms can be debilitating
Unable to function
Sleep or flushes?
Impacts on partners and children
Unable to have intercourse due to vaginal dryness/atrophy
Menopause and mood

- Perimenopausal depression is common
- Risk of new onset depression increases two fold
- Previous depression strongest predictor of depression during midlife years
- The role of estrogen deficiency vs sleep deprivation in altering mood and cognitive function is debated
- Anxiety and sleep.

Sciller et al. Comprehensive physiology 2016
Worsley et al., Maturitas 2014 77(2):111-7
Gibbs et al., Women Health Issues 2013 23(5):301
Peri-menopausal Depression

- Take a good history
- You may be the only ones seeing these women regularly
- Be aware of increased risks of mood disturbance
- Check other causes
Treating depression with estrogen?

- 57 women with depression. (CESD 27-29) RCT oestradiol vs placebo mean age 60. No difference in depression scores after 8 weeks (Morrison 2004).

- 50 women RCT oestradiol vs placebo mean age 50. Remission of depression occurred in 17 (68%) of women on oestradiol compared to 5 (20%) on placebo (Soares 2001).

- Women with past PMD treated with HRT showed increased depression when HRT was withdrawn (RCT) (Schmidt 2015 Jama Psych).
Prevention

Does 12 months transdermal oestradiol and progesterone prevent development of depression compared to placebo? (RCT)

- 172 peri-menopausal and post menopausal women
- 32.3% of women using placebo developed clinically significant depressive symptoms compared to 17.3% of women on oestrogen
- Is it a preventative treatment?

Gordon FEB 2018 JAMA Psychiatry
Oestrogen and Psychiatric disorders

- Menopause associated with a worsening of Bipolar illness (Marsh 2012)
- Comorbidity between PMDD and BD is associated with worse clinical outcomes and increased illness burden. (Slyphenko 2017)
- Oestrogen (adjunct) versus placebo for women with schizophrenia: *Cochrane protocol June 2016*
Management of menopause
THE TRUTH ABOUT HORMONES

Hormone-replacement therapy is riskier than advertised. What’s a woman to do?
Menopausal Hormone Therapy

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

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

**Risks:**
- Age related – CVA/VTE, stroke, gallbladder
- Progestogen related – breast cancer
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
Menopausal Hormone Therapy

- The most effective treatment for symptom control- 7-21 days
- There is no consistent formula that works for every woman.
- Adjustment of doses is critical
- Mood improves in 68-80% of women
Surgical Menopause

• Women with a surgical menopause may require higher doses of estrogen to settle sx

• The risks of menopause before age 45yrs are substantial. Hormone therapy should be used unless there are contraindications.

• 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
Stellate ganglion blockade
Your practice

- Be aware and proactive
- Take a good history
- ? Prescribe
- 7-21 days the magic oestrogen window
- Buddy up with someone who has an interest
- USE Australasian Menopause Society Info
BEST “PICK” Hysterectomy

- Estradot 50 (25, 50, 75, 100 micrograms estradiol per day)
- 3 to 4 week trial
- Monitor night sweats, sleep, mood, vaginal dryness
- Make a list of active problems you think may be related to hormones
Patient

- Informed consent risks and benefits
- She will tell you what's changed
- "I don’t feel myself" "Rage"
- Ask about QoL
- Talk about hormones and mood and see if she wants to try hormones for a month.
- They will either work or not
- Check your list when she returns
Informed consent

- Risks and benefits
- Australasian Menopause Society pamphlets
- Clotting
- Breast cancer (? Increased)
- All about seeing if this change in mood/ psych state is being affected by the “co-morbidity of menopause”
Best PicK: No hysterectomy

- Estradot
- Utrogeston 100mg (micronised progesterone)
- Explain risks, benefits and side effects
- Bleeding (17%) will bleed in the first year
Why prescribe

- Will find out if the cause of the mood upset is hormonal
- If it works (“like a light going on” - a switch! Back to normal!)
- Familiarise yourself with the local doctors that have expertise in this area. (AMS site www.menopause.org.au)
Take home messages

- Hormones have significant effects on neurotransmitters and mood
- Individual women have increased vulnerability to normal hormone changes
- A rocky menopause superimposed over an existing psychiatric illness may increase morbidity
Practical Approach

- Think hormonal soup
- Across the life cycle
- Identify those women at risk
- Be pragmatic
- Trial appropriate treatment - 28 days!
Final Thoughts

1. Trial of HRT if you feel depression or relapse is related to menopause.

2. Think about reproductive mood disturbance in the life course-post partum, premenstrual and post menopausal

3. Be proactive- have a plan for all women as they age

4. Treatment and prevention?
Quality of Life
Kia Ora

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Women’s Health Research

Research making a difference to women