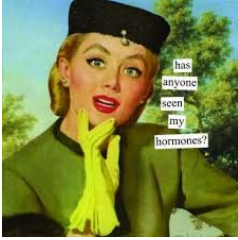


Menopause and Mood

**Women's health across the lifespan
GP symposium, Epworth, June 4 2016**


Dr Roisin Worsley, FRACP
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

Harlow SD, Gass M, et al. Climacteric. 2012

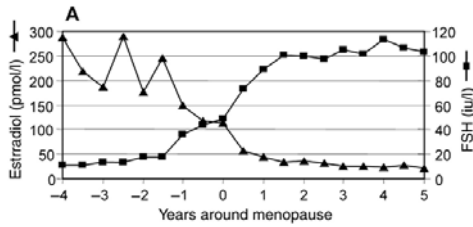


	Menarche												FMP (0)			
Stage	-5	-4	-3b	-3a	-2	-1	+1 a	+1b	+1c	+2						
Terminology	REPRODUCTIVE				MENOPAUSAL TRANSITION				POSTMENOPAUSE							
	Early		Peak		Late		Perimenopause		Early		Late					
Duration	variable				variable		1-3 years		2 years (1+1)		3-6 years		Remaining lifespan			
PRINCIPAL CRITERIA																
Menstrual Cycle	Variable to regular	Regular	Regular	Subtle changes in flow Length	Variable Length Persistent >7-day difference in length of consecutive cycles	Interval of amenorrhea of >60 days										
SUPPORTIVE CRITERIA																
Endocrine			Low	Low	Variable Low	Variable Low	>25 IU/L**	Variable Low	Stabilizes	Very Low	Very Low					
FSH			Low	Low	Low	Low	Low	Low	Very Low	Very Low						
AMH			Low	Low	Low	Low	Low	Very Low	Very Low							
Inhibin B			Low	Low	Low	Low	Low	Very Low	Very Low							
Antral Follicle Count																
DESCRIPTIVE CHARACTERISTICS																
Symptoms									Vasomotor symptoms Likely	Vasomotor symptoms Most Likely	Increasing symptoms of urogenital atrophy					

* Blood draw on cycle days 2-5 † = elevated
**Approximate expected level based on assays using current international pituitary standard¹⁴⁹

Medscape! Source: Menopause © 2012 The North American Menopause Society

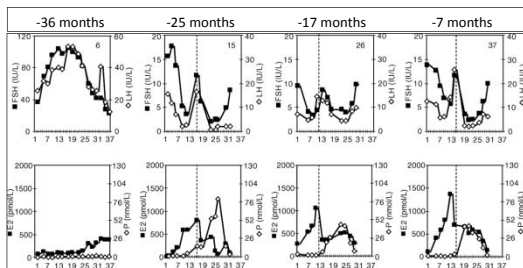
Hormones across the menopause transition



Burger et al Human Reprod Update 2007



One woman's hormones in the months prior to menopause



Burger et al Menopause 2008



Menopausal symptoms

- 1 in 3 women have severe psychological symptoms
- 1 in 4 have severe physical symptoms



Mishra GD, Kuh D. BMJ 2012



Menopausal symptoms

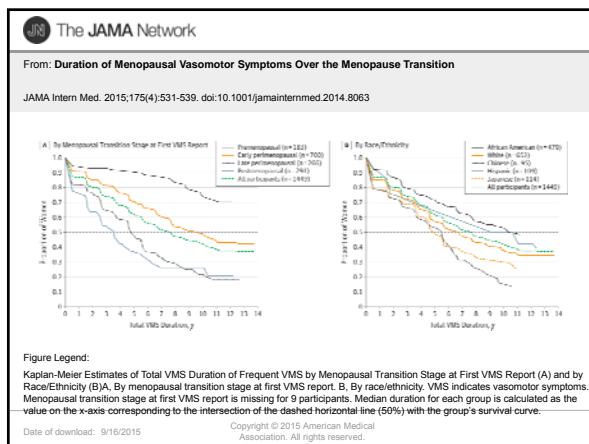
- Vasomotor symptoms (hot flushes and night sweats)
- Vaginal dryness
- Sleep disturbance
- Headaches
- Joint pain
- **Mood changes**



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



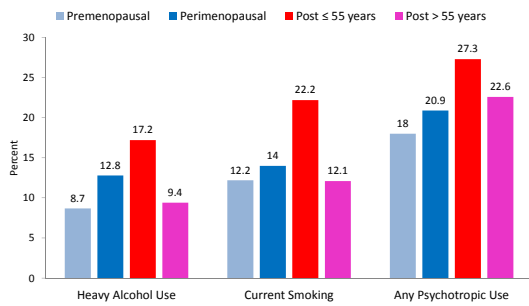


Depressive and anxiety symptoms

- 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

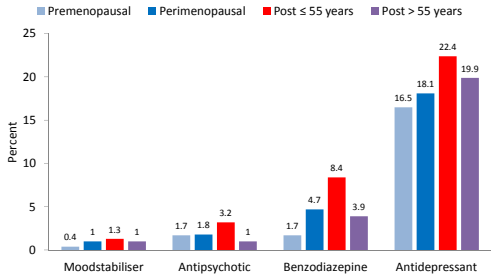


Current smoking and alcohol use

- 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



Change in case number per 1000 women per 5 years of treatment in women aged 50-59

	Estrogen + Progestin	Estrogen only
All cause mortality	-5.3	-5.0
CHD	-0.9	-3.8
Breast Cancer	+6.8 (NAMS +8 per 10,000)	-1.5
Venous thromboembolism	+5	+2
Stroke	+1.0	+1.2
Fracture	-4.9	-5.9
Cholecystitis (all ages)	+9.6	+14.2
T2DM	-11	-11
Colorectal cancer	-1.2	0

Taken from Martin et al Menopausal Hormone therapy: benefits and risks. Uptodate July 2015



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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



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Menopause and pre-existing mental illness

- Bipolar Disorder
 - More depressive symptoms Marsh et al Bipolar Disord 2012
 - ?Hormone therapy helpful Freeman et al J Clin Psych 2002
- Schizophrenia
 - ?worse mood/QoL ?improvement w age Seeman, Maturitas 2012
- Depressive Disorders
 - Recurrence more common Payne et al, J Aff Dis 2002



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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



Fatigue



Irritability



Bloating



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Anxiety



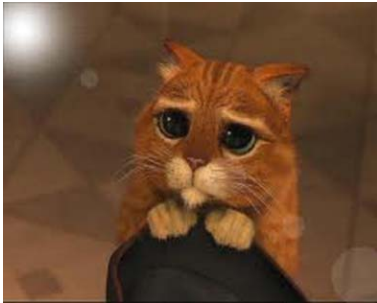
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Cravings



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Low mood



Common symptoms of PMS

- | | |
|-------------------|---------------------------|
| Fatigue | Increased appetite |
| Irritability | Oversensitivity |
| Bloating | Swelling |
| Anxiety/tension | Expressed anger |
| Breast tenderness | Crying easily |
| Mood lability | Feeling of isolation |
| Depression | Headache |
| Food cravings | Forgetfulness |
| Acne | Gastrointestinal symptoms |
| | Poor concentration |
| | Hot flashes |
| | Heart palpitations |
| | Dizziness |

Mortola, JF, Girton, L, Beck, L, Yen, SS. Diagnosis of premenstrual syndrome by a single prospective reliable instrument. *Obstet Gynecol* 1990; 76:302. Reprinted with permission from the American College of Obstetricians and Gynecologists (Obstetrics and Gynecology, 1990; 76:302). FROM LIPPINCOTT.



Premenstrual dysphoric disorder

- PMDD diagnosis focuses on mood



- 5-10% women reproductive age

C. Guille et al. / *Epilepsy & Behavior* 13 (2008) 12-24



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

C. Guille et al. / Epilepsy & Behavior 13 (2008) 12–24



Tests

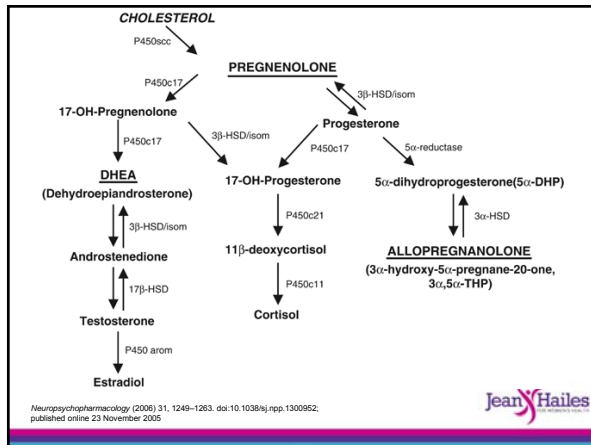
- No diagnostic tests
- Look for:
- Other illnesses – thyroid
 - Menopause transition
 - Other mood disorder
 - Current medications



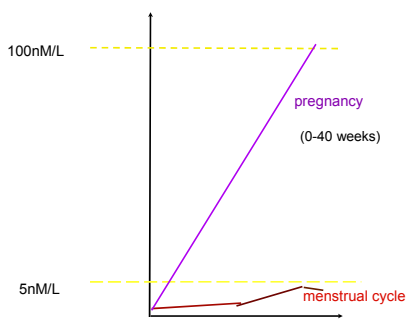
? cause

- 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



Compiled from: Maguire, Psychoneuroendocrinology (2009) 34, 584–590; Luisi, S. et al. J Clin Endocrinol Metab 2000;85:2429-2433; Gemazzani, A. R. et al. J Clin Endocrinol Metab 1998;83:2099-2103



ALLO in PMDD ? A paradoxical response

Andreen et al. Sex steroid induced negative mood may be explained by the paradoxical effect mediated by GABA_A modulators. *Psychoneuroendocrinology* (2009)

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Neuropsychopharmacology

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

Figure 3

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Treatment - lifestyle

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

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Treatment - over the counter

- ?calcium
- ?Vitex agnus castus (Chasteberry)
- ?Other herbs: St John's Wort



Treatment - medication

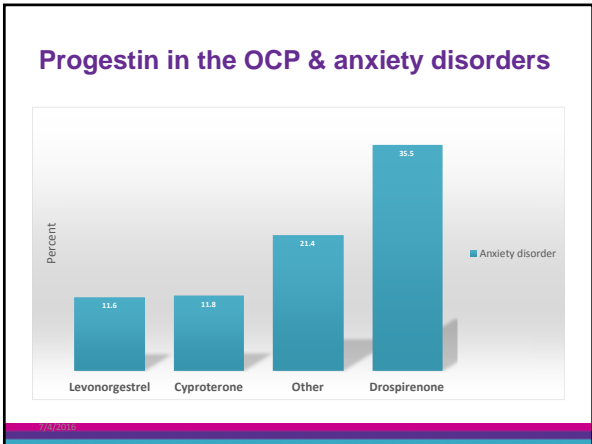
- Oral contraceptive pill use continuously (take sugar pills every three months)
- Antidepressants (SSRIs) help brain to better respond to hormonal fluctuations
- Other

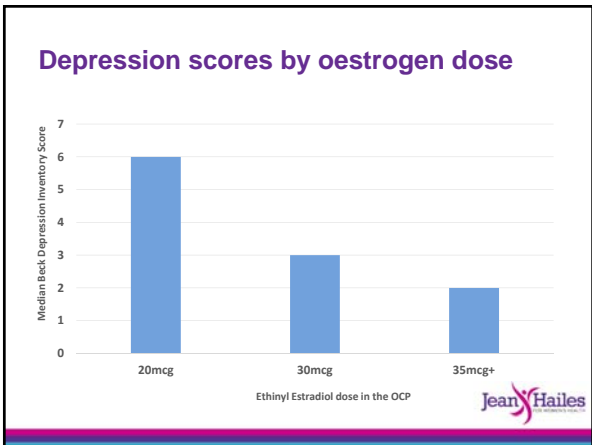


The oral contraceptive pill

- Estrogen + progestin
- High discontinuation rate due to mood side effects
- Progestins cause worse mood in some women







Choosing an OCP

- It's difficult!
- Mood SEs with OCP I like:
 - Zoely
 - Qlaira
 - Valette
- & I avoid Yaz/Yasmin

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14/06/15

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