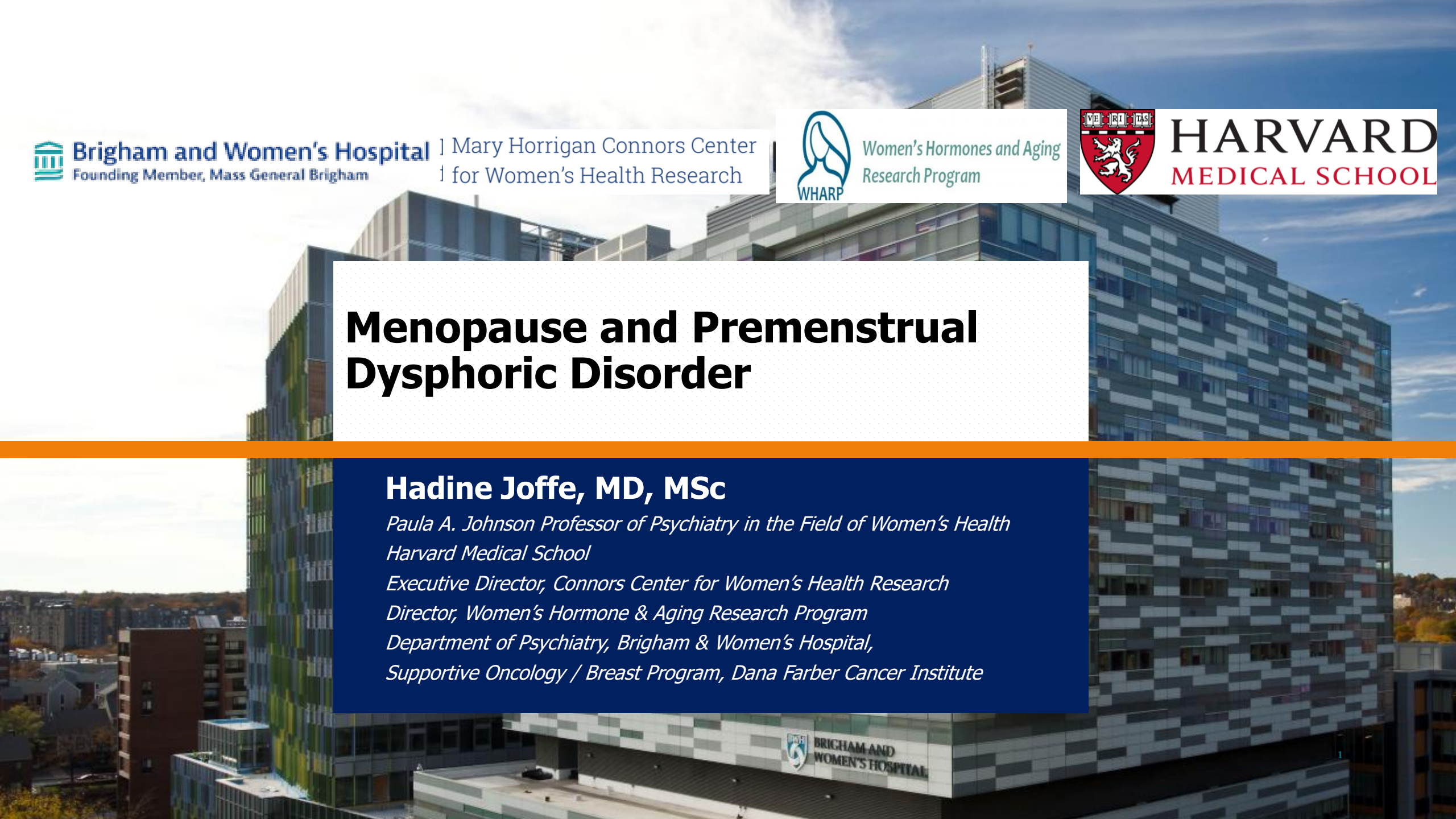

Brigham and Women's Hospital
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Menopause and Premenstrual Dysphoric Disorder

Hadine Joffe, MD, MSc

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DISCLOSURES

- Grant support to research program:
  - NIH / National Institute of Health
  - Wellcome Trust
  - Merck
- Consultant/Advisory:
  - Bayer
  - Novo Nordisk
- IND to use leuprolide in healthy volunteers
- Spouse:
  - Employee: Arsenal Biosciences employee
  - Equity: Merck Research Labs

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Brigham and Women's Hospital/Harvard Medical School

Learning Objectives

1. Describe prevalence, course and common precipitating and co-occurring factors of major depression and subthreshold depressive symptoms across menopause transition

2. Understand premenstrual dysphoric disorder and premenstrual exacerbation of mood disturbance

3. Review treatment options for mood disturbance related to menopause and the premenstruum

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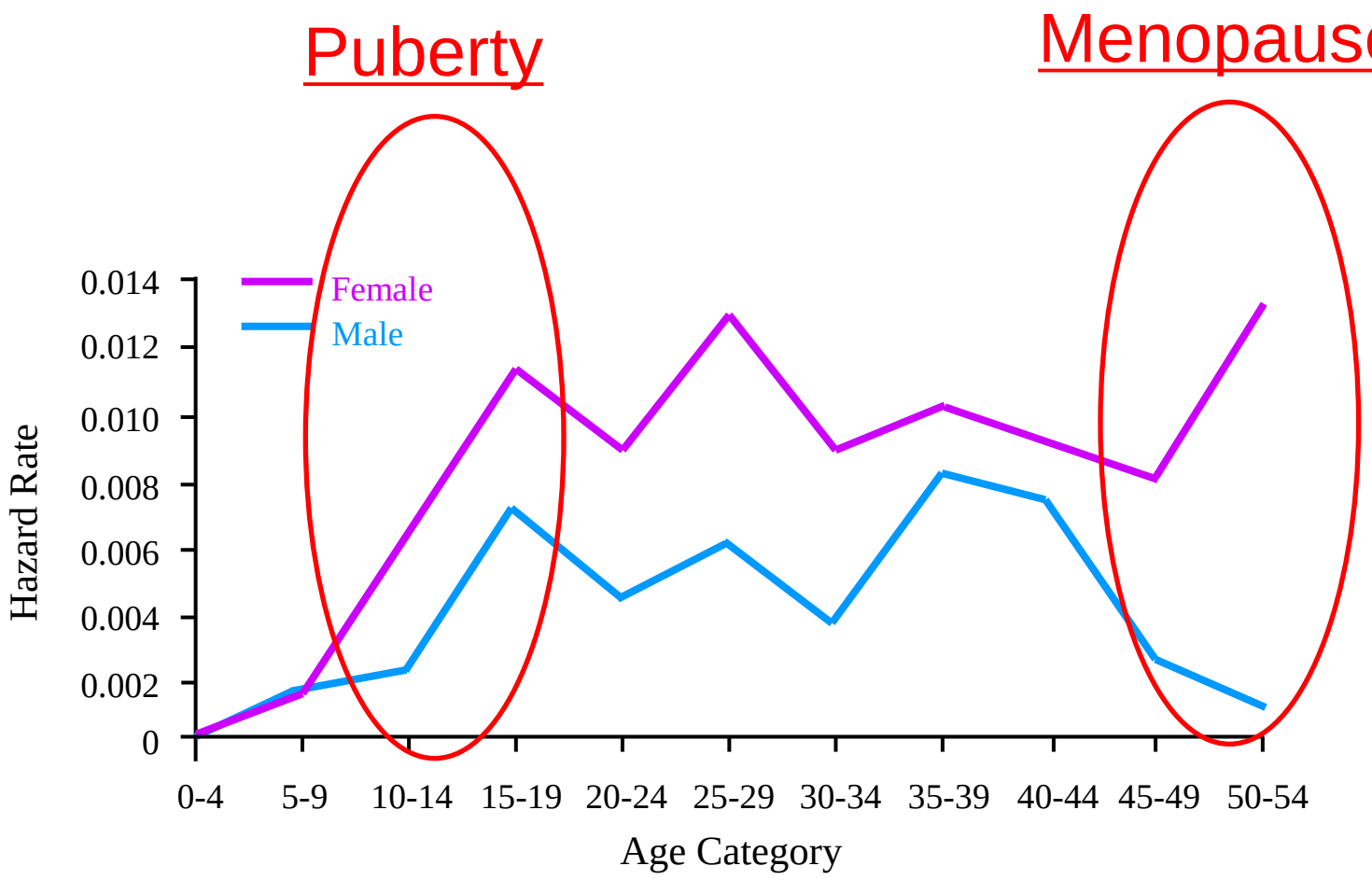
♀ vs. ♂: 2x lifetime risk of depression

World Health Organization Mental Health Surveys
Association of gender with lifetime risk of DSM-IV depression
(15 countries, n=73,099)

		All countries combined
		F:M OR (95% CI)
I. Mood disorders		
Major depressive disorder	♀ vs. ♂	1.9* (1.8–2.0)
Dysthymic disorder		1.9* (1.6–2.2)
Bipolar disorder		0.9 (0.8–1.0)
Any mood disorder		1.8* (1.7–1.8)

Seedat S, *JAMA Psych* 2009

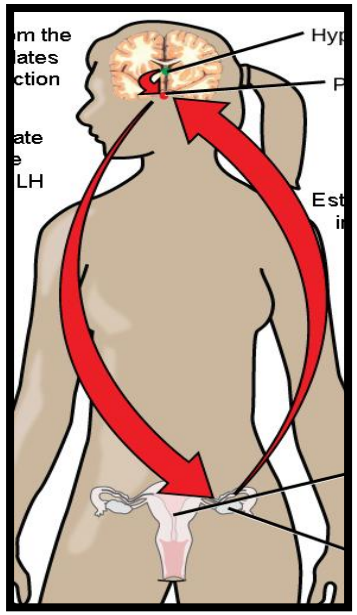
Risk of major depression by age in ♀ and ♂



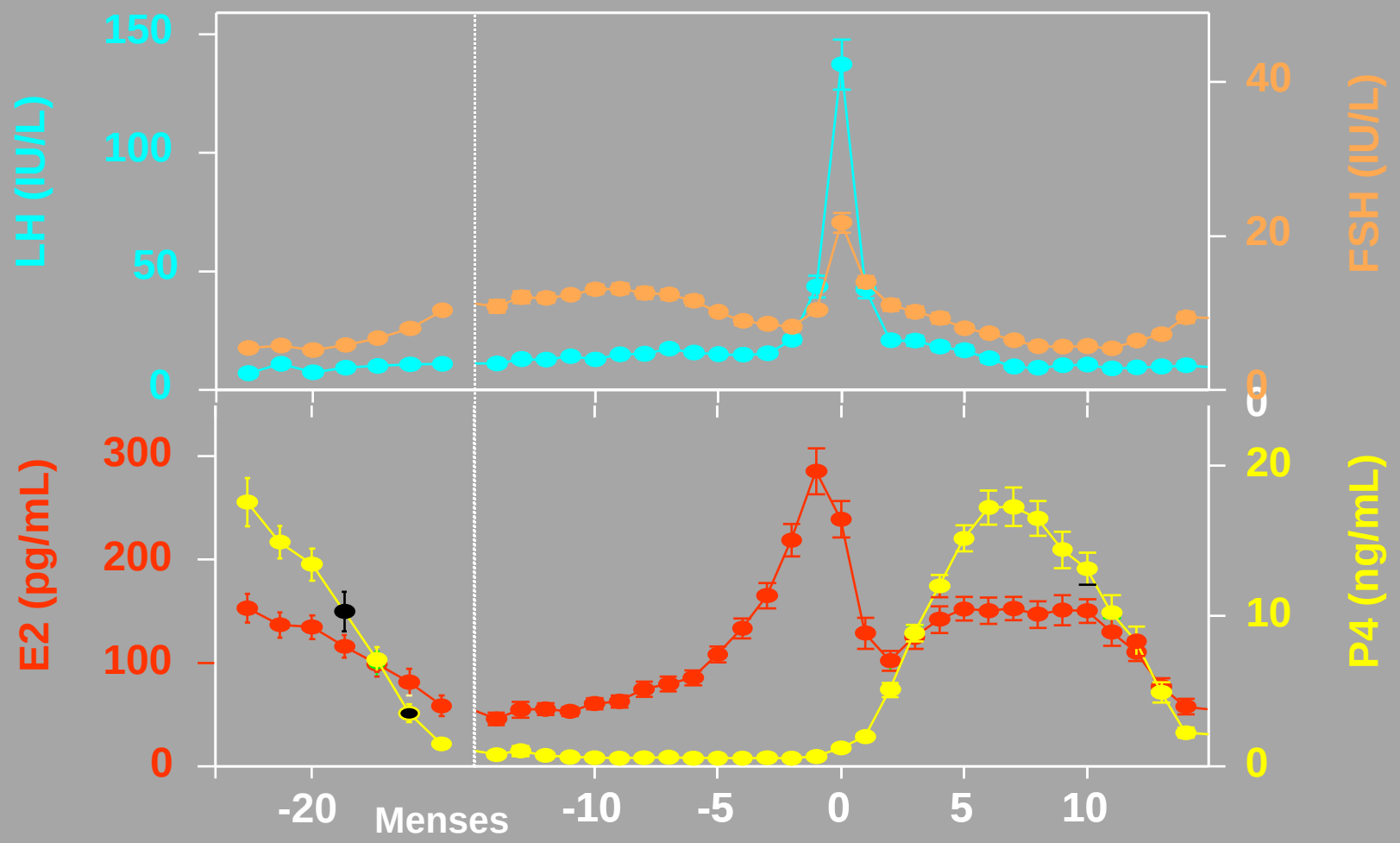
Kessler R. *J Affect Disord.* 1993

What explains excessive risk of depression in women?

1. Endorsement of symptoms
2. Gender roles, socio-cultural biases, economics
3. Genetics
4. Inflammation
5. Stress exposure & response
6. Reproductive transition-related risk factors
7. Sex hormones
8. Neurosteroids

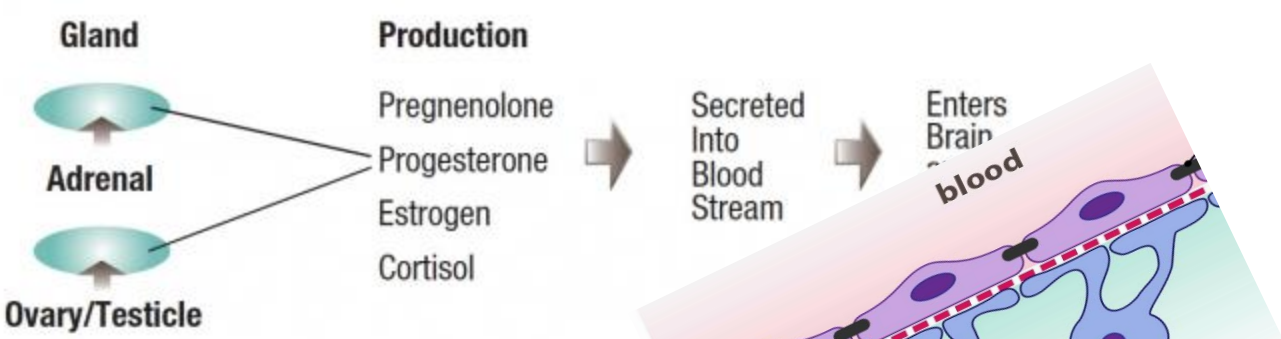


Reproductive hormone changes across the menstrual cycle



Neurosteroids:
Sources of female reproductive hormones

Extra-CNS production



Intra-CNS production

Estradiol
Progesterone
Allopregnenolone

Menopause


OUT OF ORDER


depression
estrogen
stop
senior
lifestyle
Menstrual
progesterone
uncomfortable
menopause
stress
woman
estrogen
hormones
mature
menopause
healthcare
lifestyle depression
pensioner
sweat
stress
middle
old
heat
periods
worried
aged
periods
progesterone
woman
menstruation
health

Perimenopause and depression

CONSENSUS RECOMMENDATIONS

Menopause: The Journal of The North American Menopause Society
Vol. 25, No. 10, pp. 1069-1085

Guidelines for the evaluation and treatment of perimenopausal depression: summary and recommendations

Pauline M. Maki, PhD,[1] Susan G. Kornstein, MD,[2*] Hadine Joffe, MD, MSc,[3] Joyce T. Bromberger, PhD,[4] Ellen W. Freeman, PhD,[5] Geena Athappilly, MD,[6] William V. Bobo, MD, MPH,[7] Leah H. Rubin, PhD,[8] Hristina K. Koleva, MD,[9] Lee S. Cohen, MD,[10] Claudio N. Soares, MD, PhD, MBA,[11] on behalf of the Board of Trustees for The North American Menopause Society (NAMS) and the Women and Mood Disorders Task Force of the National Network of Depression Centers*

Menopause terms & definitions

Menopause marks end of reproductive potential

Perimenopause

Irregular, unpredictable, then infrequent menstrual cycles

Begins ~48 years

Last ~4 years

Menopause

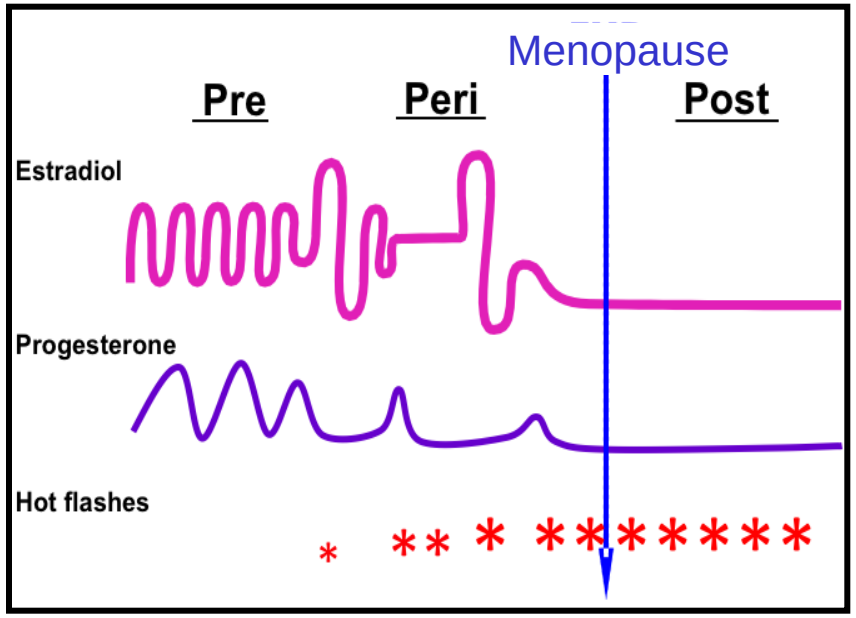
=12 months without menses

Age ~52 years

Postmenopause

More than 12 months past final menstrual period

Hormone changes across menopause

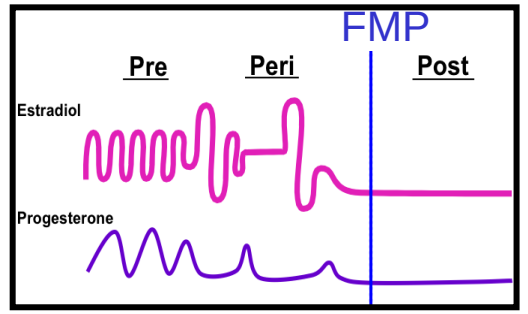


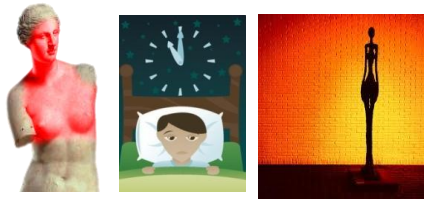
Pre/peri/postmenopausal

FMP = final menstrual period

Most common symptoms of menopause definition

1. Menstrual cycle irregularities and bleeding abnormalities
2. Thermoregulatory disturbance: hot flashes, night sweats, vasomotor symptoms (VMS)
3. Sleep interruption
4. Mood: depressive symptoms >> major depression
5. Vulvo-vaginal and urinary symptoms





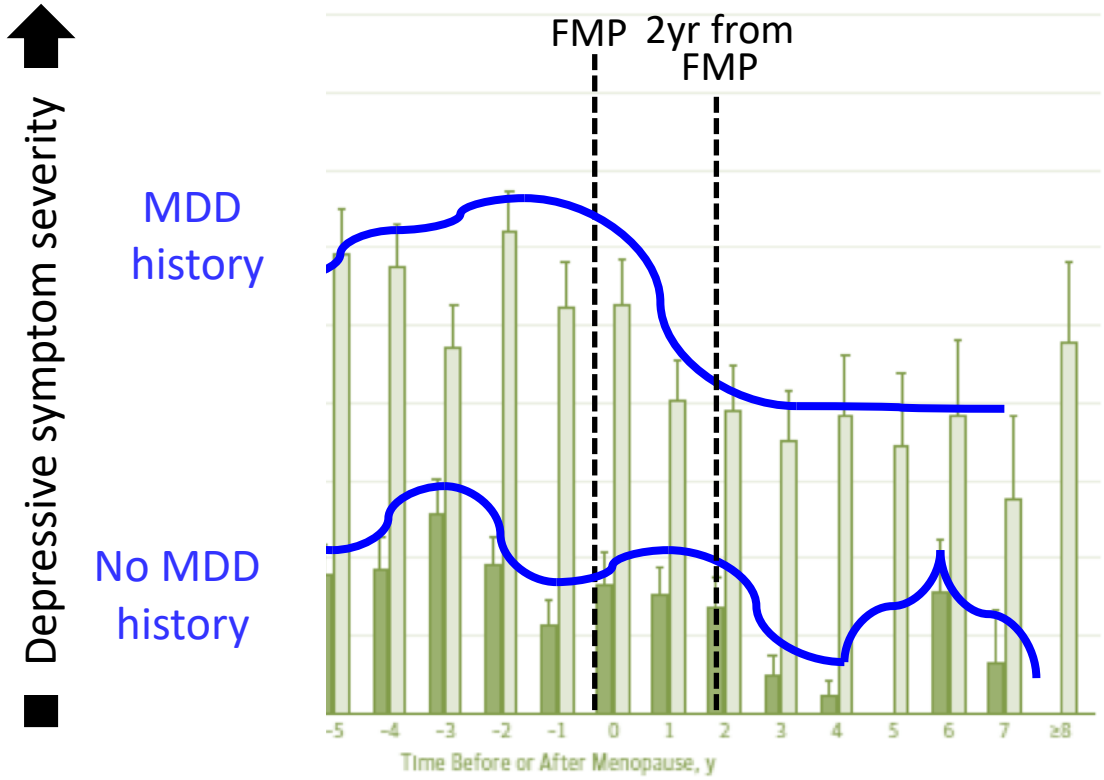
Menopause transition is a period of vulnerability for depression in women: doubling of risk of depression of peri/early post

1. ↑ risk of depressive symptoms in peri & early post
2. ↑ risk of clinical depression in peri & early post
3. ? ↑ risk of 1st lifetime onset of clinical depression in peri & early post
   - Data are mixed

Brown L, *Lancet* 2024; Freeman E, *Arch Gen Psych* 2006; Cohen LS, *Arch Gen Psych* 2006 ; Bromberger JT & Kravitz HM. *Obstet Gyn Clinics* 2011; Harlow, *Am J Epidemiol* 2013; Bromberger JT, *Psychol Med* 2014

Perimenopause is a Transient Period of Risk for Depressive Symptoms in Subset of Women

Good News!

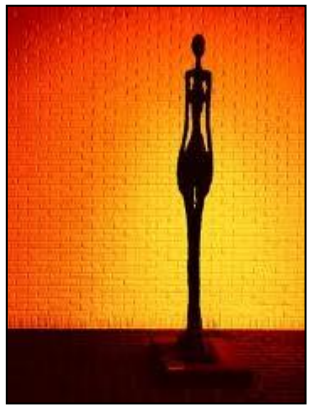


1. <u>High baseline depression symptoms</u>: Trajectory toward improved mood across and after FMP slows transiently surrounding the FMP
2. <u>Low baseline depression symptoms</u>: Vulnerability to small increase in depressive symptoms across FMP

MDD = major depressive disorder
FMP = final menstrual period

Freeman, *JAMA Int Med* 2014; Avis, *J Aff Dis* 2024

Mood Disturbance Across Menopause Transition

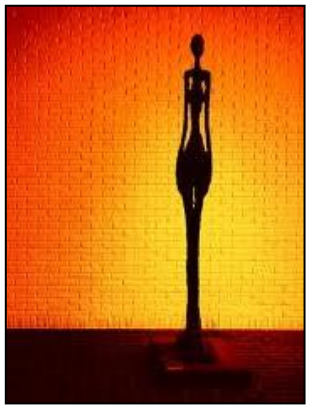


- Major Depressive Disorder (MDD)

- 2.7x risk within-person risk as progress into perimeno
- No increased risk of first-lifetime episode of MDD
  - When present, linked with VMS and stressful life events
- Greater risk if
  - Psychiatric risk factors
    - History of MDD
    - Anxiety
    - Medical illness
  - Menopause/hormonal risk factors
    - Sleep disruption

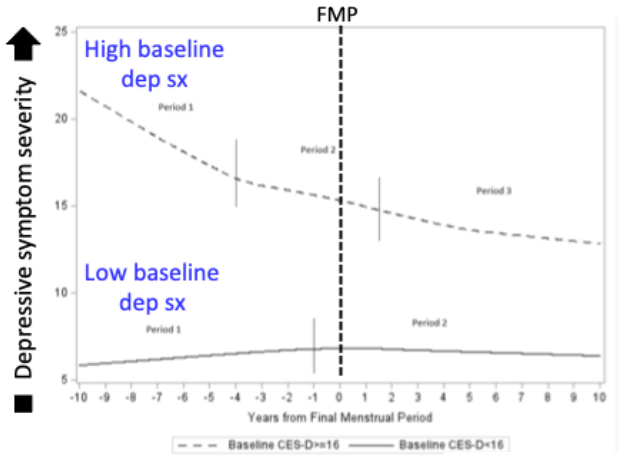
Bromberger. *Psych Med* 2015; Freeman. *Arch Gen Psych Med* 2006

Mood Disturbance Across Menopause Transition



Depressive Symptoms

- 17-28% in perimeno vs. 14-21% in late premeno for entire population
- 2-4x risk within-person risk as progress into perimeno
- Greater risk if
  - Psychosocial risk factors
    - History of MDD
    - Stressful life events, financial stress, low social support
    - Racial minority, higher BMI, smoking, lower activity levels
  - Menopause/hormonal risk factors
    - Reproductive hormone dynamics
    - Longer time in perimenopause
    - Hot flashes
    - Sleep disruption



Subgroup problem

Risk factors in **high** baseline CESD group:
↓social support, ↓FSH, ↓estradiol,
↑sleep disturbance

Risk factors in **low** baseline CESD group:
↑anxiety, stressful life events, ↓BMI,
↓role-physical function

Maki. *Menopause* 2018; Brown. *Lancet* 2024; Avis. *J Aff Disorders* 2024

Depression not universal: A subgroup problem


THE LANCET

Series

Menopause 3

Promoting good mental health over the menopause transition


The Washington Post

Democracy Dies in Darkness

Subscrib

Depression risks of menopause have been overstated, study finds

By Caren Chesler

Updated March 5, 2024 at 7:40 p.m. EST | Published March 5, 2024 at 2:14 p.m. EST


The Harvard Gazette

Menopause depression risk has been exaggerated

March 11, 2024

Some groups are more vulnerable but symptoms far from universal, review finds

The trade off

- Empowerment
- Anticipation, fear
- Preparation
- Education
- Cross-sectional attribution
- Implication for treatment

Brown. *Lancet* 2024

How do you know if depression occurring in peri/postmenopausal woman is related to her being peri/postmenopausal?

True, true, related?

True, true, unrelated?

Clinical considerations when evaluating contribution of menopause to depression

1. Depressive symptoms vs. clinical depression
2. Extent of interference with function
3. Past history of depression
4. Co-occurring / precipitating stressful life events
5. No diagnostic test or hormone profile to establish association
6. Presence of / temporal relationship to
   - Menstrual pattern changes
   - Hot flashes & night sweats
   - Associated sleep interruption
7. Sleep disturbance
   - Brief awakenings only
   - Early morning awakening

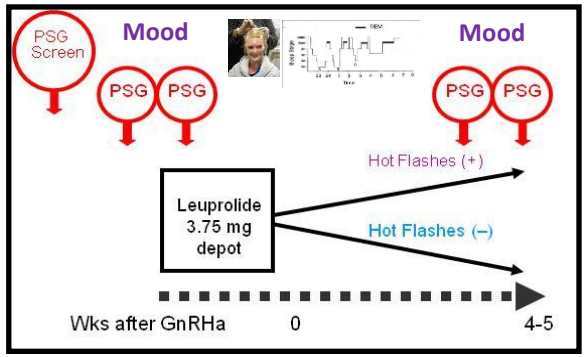
True, true, related?

True, true, unrelated?

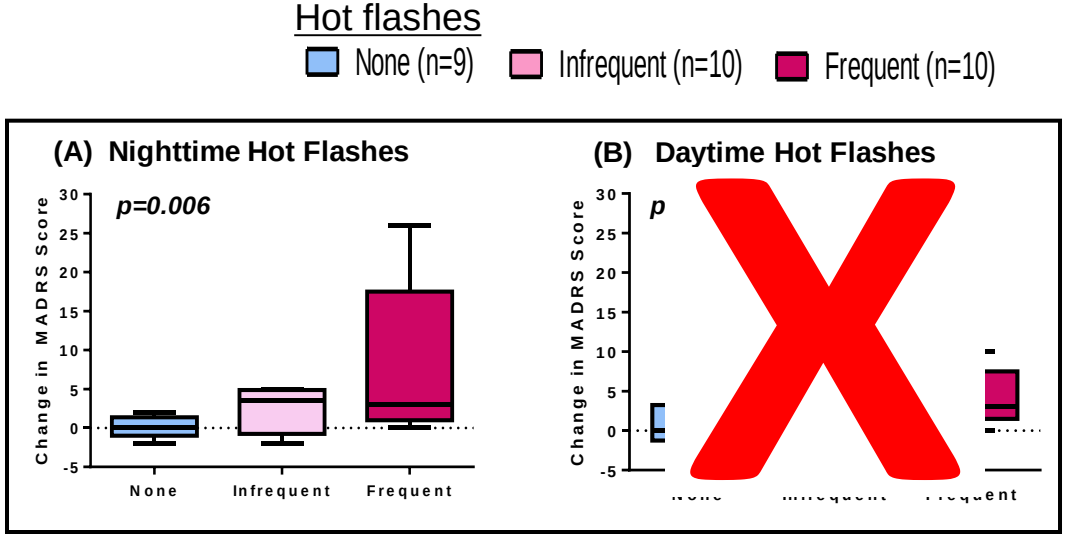
Effect of nighttime hot flashes and sleep disruption on depressive symptoms

Hot flashes → Depression

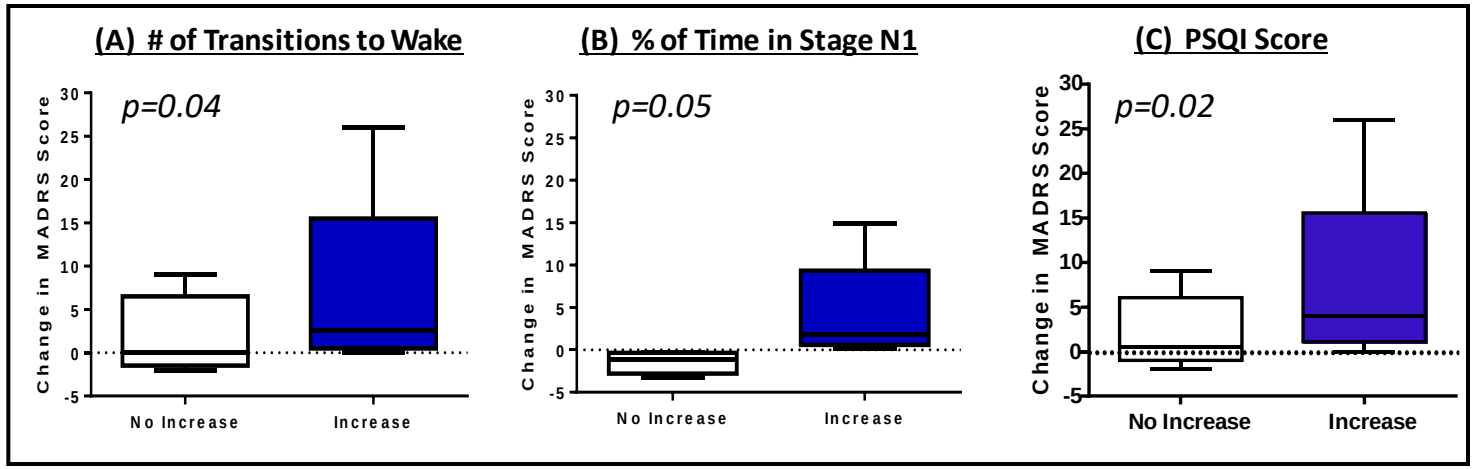
Sleep → Depression



Nocturnal, but not daytime, hot flashes, result in an increase in depressive symptoms

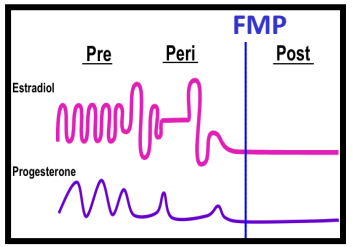


Worsening of sleep fragmentation and sleep quality result in an increase in depressive symptoms



Joffe, *J Clin Endo Metab* 2016

Reproductive hormone dynamics concurrent with perimenopause-associated depressive symptoms



Depression

Clinical studies show that mood is better as ovarian activity is more normalized in perimenopausal women.

Conversely, the more abnormal the hormonal profile, the worse the mood.

MADRS = Montgomery Asberg Depression Rating Scale

Joffe H, *J Clin Endo Metab* 2020

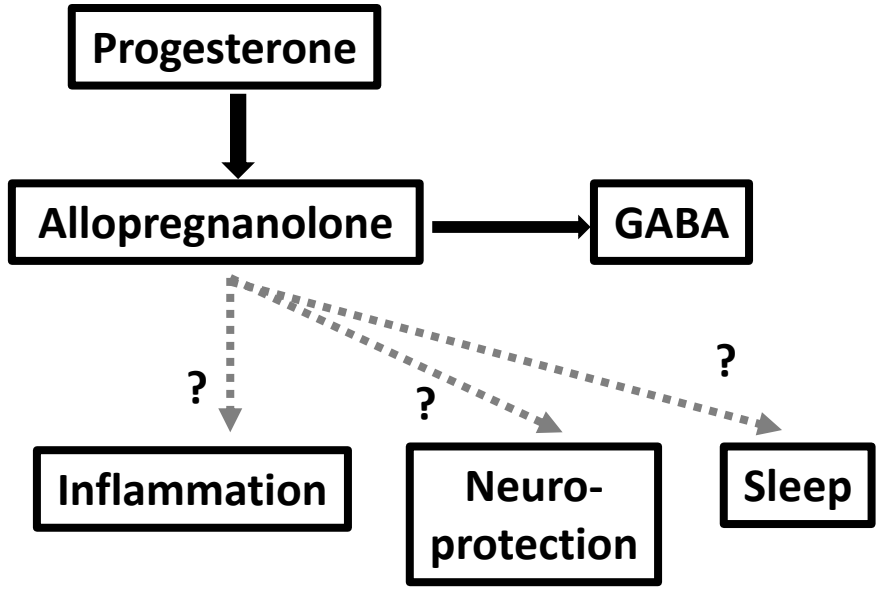
Susceptibility to hormonal contributors to menopause-related depressive symptoms

Why do some but not others develop depressive symptoms during menopause transition?

Possible explanations

1. Depressive symptoms ebb and flow based on recent/current reproductive hormone profile
2. Genetic susceptibility?
3. Stress mediation?
4. **Allopregnanolone (ALLO): metabolite of progesterone**
   - → **Extrapolating from data in postpartum depression**
   - → **ALLO is therapeutic**

As progesterone declines, does ALLO transmit perimenopausal depressive symptoms through



Joffe, *J Clin Endo Metabol* 2020; Gordon, *JAMA Psych* 2018; Schweizer-Schubert, *Front Med* 2020; McEvoy and Osborne, *Int Rev Psych* 2019;

Joffe and Burdick (MPI): R01MH128617

Pharmacotherapy approaches: menopause-associated depression and associated physical symptoms

	VMS	VMS comments	Sleep (2nd VMS)	Mood
Hormonal	Menopause-dose estrogen therapy and/or progesterone therapy Hormonal contraceptives TSEC (CEE+SERM)	Only menopause HT and TSEC FDA approved	Modest benefit	Hormonal therapy improves mild depressive symptoms; some evidence for MDD; not first-line therapy for MDD
Psychotropic or "non-hormonal"	SSRI, SNRI, gabapentin, pregabalin	Only paroxetine FDA approved	Zolpidem and eszopiclone (FDA dosing guidance), DORA (suvorexant) effective	SSRI, SNRI effective; other antidepressants not tested
Novel compounds (neurokinin B antagonists)	Fezolinetant – NK3 antagonist Elinzanetant – NK3 and NK1 antagonist	Only fezolinetant FDA approved	Elinzanetant improves sleep in women with VMS Fezolinetant without sleep benefit	No data for MDD or depressive symptoms; improve QOL
Behavioral alternatives	CBT for VMS	Reduces distress/bother	CBT for VMS-insomnia effectives	CBT not tested in this population

TSEC = tissue selective estrogen complex = conjugated estrogens + SERM (selective estrogen receptor modulators (bazedoxifene))
DORA = dual orexin receptor antagonist; CBT = cognitive behavioral therapy; QOL = quality of life

McCurry, *JAMA Int Med* 2016; Guthrie, *Sleep* 2018; Enrud, *Sleep* 2025; Lederman, *Lancet* 2023; Pinkerton, *JAMA* 2024

Treatment of depression in women with VMS

In women with VMS, approaches to major depression differ from approaches to depressive symptoms

Major/clinical depression

- Pharmacotherapies
  - ✓ Antidepressants (SSRI, SNRI, etc)
  - ✓ Interventional approaches (e.g., TMS, esketamine, ECT, hospitalization)
  - ? Neurosteroids (allopregnanolone, ganaxolone)
  - ✓ HT is not a first-line approach
    - May consider if peri, prominent VMS, no contra-indications
    - RCT used 0.1 mg TD
- Psychotherapy

Subthreshold depressive symptoms

- Pharmacotherapies
  - ✓ Antidepressants (SSRI, SNRI, etc)
  - ✓ Hormone therapies (if prominent VMS):
    - RCT used CEE 0.45mg/d + cyclic prog. 200mg/d
  - ? Neurosteroids (allopregnanolone, ganaxolone)
  - ? N
- Psych

R01MH12861 testing ALLO mechanisms

Summary of HT to treat mood

- ✓ HT (off-label) considered for subthreshold depressive symptoms when hot flashes are prominent/bothersome
- ✓ HT not 1st line for major depression

Gleason, *PLoS Med* 2015; Kornstein, *J Clin Psych* 2010; Joffe, *J Clin Psych* 2007; Joffe, *J Women's Health Gend Based Med* 2001; Soares, *J Clin Ps* 2003; Dias, *Menopause* 2006; Kornstein, *Menopause* 2014; Kornstein, *JCP* 2014; Soares, *Arch Gen Psych* 2001; Schmidt, *Am J OBGYN* 2000; Gordon, *JAMA Psych* 2018; Morrison, *Bio Psych* 2004

olled trials; TD = transdermal

TMS = transcranial magnetic stimulation, ECT = electroconvulsive therapy

Summary: Depression during peri/postmenopause

1. **Mood disturbance can present as major depression or mild subsyndromal depressive symptoms**

2. **Mild depressive symptoms more common during the menopause transition**
   - Subthreshold depressive symptoms associated with perimenopausal hormone profile, nighttime hot flashes, and sleep interruption, poor social support, anxiety

3. **Major depression is less common and typically represents recurrence**

4. **Hormone therapy**
   - Effective for subthreshold symptoms and for clinical depression mostly when women are perimenopausal and have hot flashes
   - Not effective for postmenopausal women without hot flashes

5. **Antidepressants are effective treatments of depression associated with the menopause transition**

Premenstrual dysphoric disorder (PMDD)

PMDD Case: Do you use SSRI or HC?

26-year-old woman presenting with PMDD symptoms

- One prior depression episode 6 years ago
- Advised against using HC because of brittle depression

<u>Questions</u>:

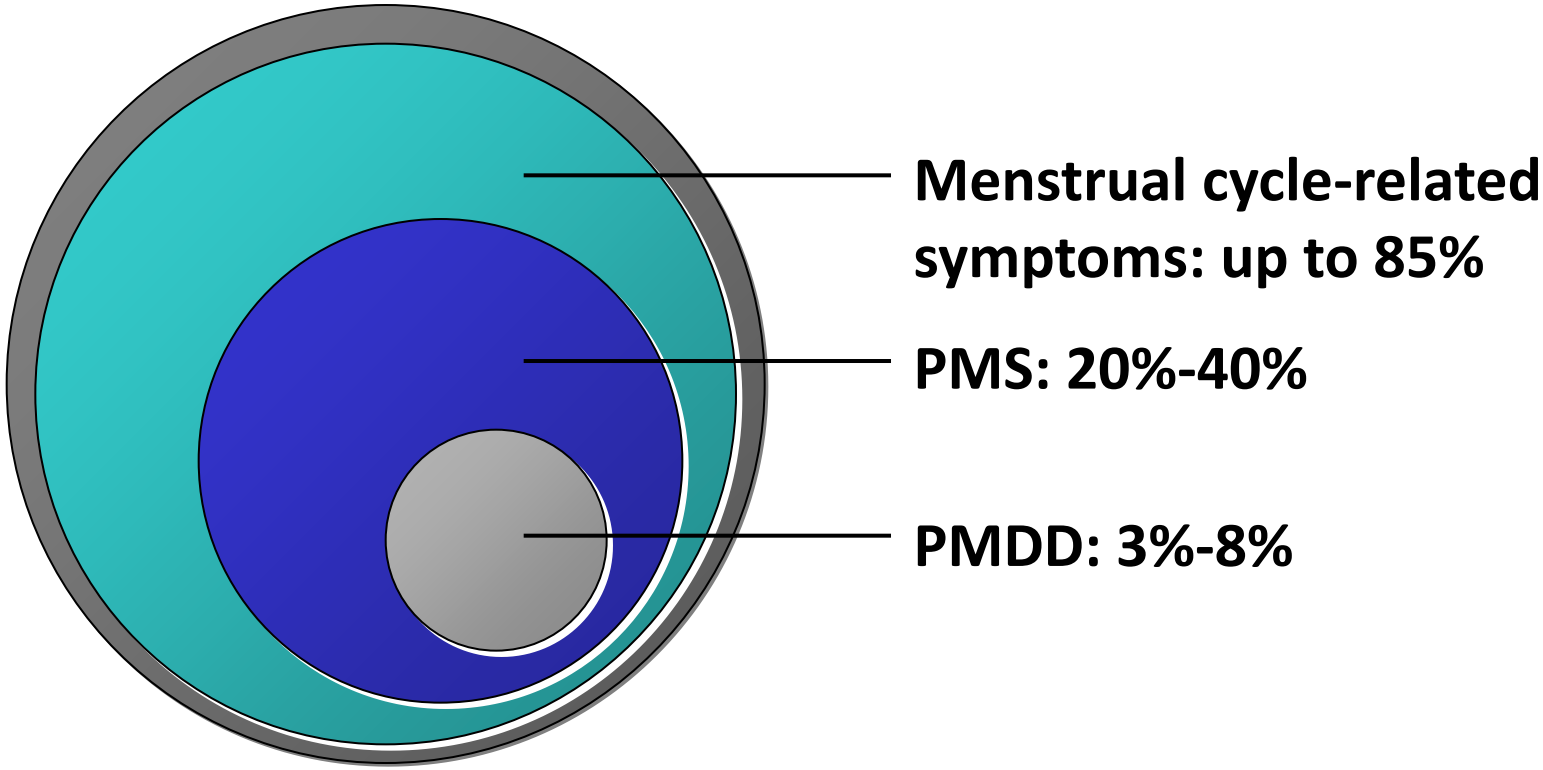
1. Should she be treated with an SSRI or an HC?

2. Can she go on HC?
   For contraception?
   For premenstrual symptoms?

HC = hormonal contraceptives

- Oral contraceptives plus other routes of administration
- Systemic (penetrating CNS)
- Local (IUD)
  - Note: vaginal ring is systemically absorbed
- Estrogens + progestin
- Progestin alone

PMS and PMDD: A spectrum of symptoms



PMS = premenstrual syndrome; PMDD = premenstrual dysphoric disorder.

A Clayton. *J Psychiatr Pract* 2008; Epperson et al. *Am J Psych* 2012

PMDD Diagnosis in DSM-5 TR

A. In most menstrual cycles during the past year, five (or more) of the following symptoms occurred during the final week before the onset of menses, started to improve within a few days after the onset of menses, and were minimal or absent in the week postmenses, with at least one of the symptoms being either (1), (2), (3), or (4):

1. marked affective lability (e.g., mood swings; feeling suddenly sad or tearful or increased sensitivity to rejection)
2. marked irritability or anger or increased interpersonal conflicts
3. markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts
4. marked anxiety, tension, feelings of being "keyed up" or "on edge"
5. decreased interest in usual activities (e.g., work, school, friends, hobbies)
6. subjective sense of difficulty in concentration
7. lethargy, easy fatigability, or marked lack of energy
8. marked change in appetite, overeating, or specific food cravings
9. hypersomnia or insomnia
10. a subjective sense of being overwhelmed or out of control
11. other physical symptoms such as breast tenderness or swelling, joint or muscle pain, a sensation of "bloating," weight gain

B. The symptoms are associated with clinically significant distress or interference with work, school, usual social activities, or relationships with others (e.g., avoidance of social activities, decreased productivity and efficiency at work, school, or home).

C. The disturbance is not merely an exacerbation of the symptoms of another disorder, such as major depressive disorder, panic disorder, dysthymic disorder, or a personality disorder (although it may co-occur with any of these disorders).

D. Criteria A, B, and C should be confirmed by prospective daily ratings during at least two symptomatic cycles. (The diagnosis may be made provisionally prior to this confirmation.)

E. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

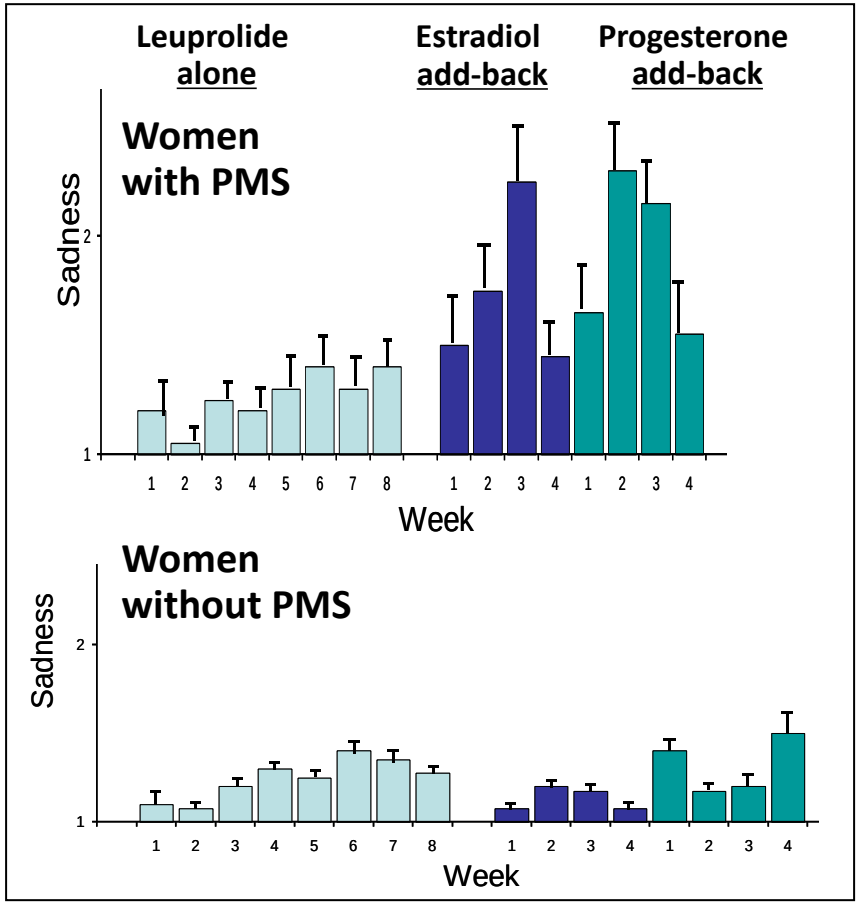
- 5+ of 11 symptoms
  - 1+ of 5 is mood symptom
- Psychological > physical symptoms
- Interfere with role functions
- Symptoms restricted to luteal-phase
  - During the week before menses and remit within days of menses
  - Establish "on and off-ness"
- Not an exacerbation of another psychiatric disorder

PMDD: Hormonal basis

- No abnormality in hormone levels[1]
- Susceptibility to fluctuation of estrogen and progesterone[2,3]
- Vulnerability may be serotonin mediated[2]
- Gonadotropin releasing hormone (GnRH) agonists are effective therapy
  - Eliminate hormonal fluctuation
  - PMS re-occurs with add-back therapy

- Role of impaired $GABA_A$-R response to dynamic ALLO fluctuations across the menstrual cycle? [4]

Recurrence of Sxs of PMS during the Addition of Estradiol or Progesterone to the Leuprolide Regimen[4]



[4] Hantsoo, Epperson. *Neurobiol Stress* 2020

[1] Rubinow DR, et al. *Psychopharmacol Bull* 1998; [2] Joffe H, Cohen LS. *Biol Psychiatry* 1998; [3] Deecher D, et al. *Psychoneuroendocrinology* 2008; [4] Schmidt PJ, et al. *N Engl Med* 1998

PMDD: Treatment options

Serotonin-based

- Cochrane Database of Systematic Reviews[1]
  - Identified 31 RCT
  - SSRIs > placebo
  - Response rates ~ 60%

Other

PMDD: cognitive behavioral therapy
PMS: benzodiazepine (alprazolam), buspirone, calcium, GnRH agonists

RCT = randomized controlled trials
VTE = venothrombotic events
OC = oral contraceptives
GnRH = gonadotropin releasing hormone

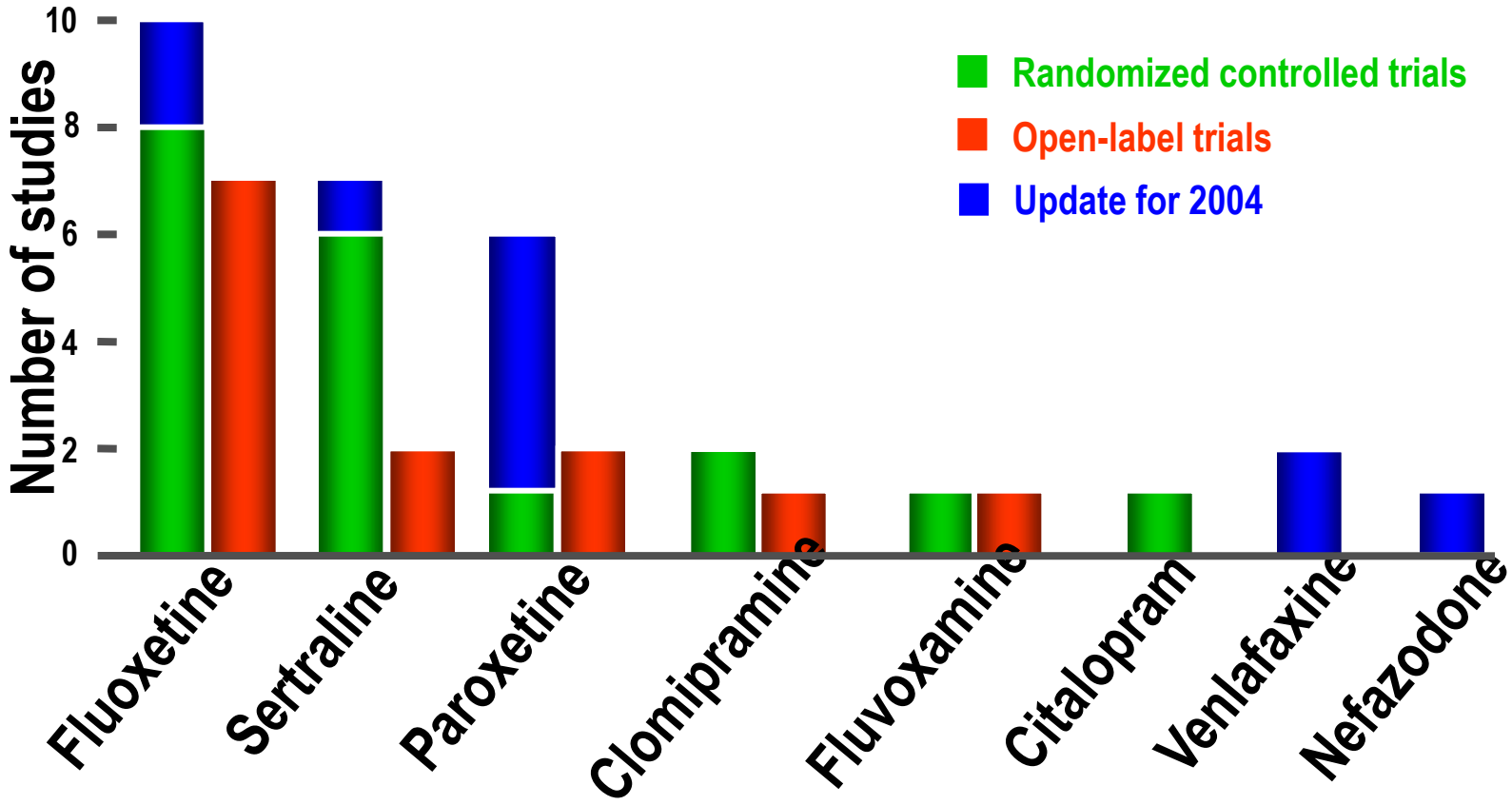
Hormone-based

- Systemic hormonal contraceptives
  - Only drospirenone / estradiol pill FDA approved[2]
    - But higher VTE risk
    - Response rate 48%[2]
- Shorter hormone-free interval (24/4 day)
  - Reduces adverse symptoms during the hormone-free interval[3]
  - Long-cycle treatment (6 month) effective [4]
- Other HC with different progestins less well studied and with conflicting results[5-7]
  - Monophasic may be more effective than triphasic OC[5]

[1] Cochrane Database Syst Rev 2002

[2] Yonkers KA, et al. *OBGYN* 2005; [3] Sulak PJ, et al. *Obstet Gynecol* 2000; [4] Coffee A, et al. *Am J OBGYN* 2006; [5] Backstrom T, et al. *Contraception* 1992; [6] Graham CA, Sherwin BB. *Psychoneuroendo* 1993; [7] Graham CA, Sherwin BB. *J Psychosom Res* 1992

Serotonergic agents shown to be effective for treating PMDD/PMS



Adapted from Dimmock PW, et al. *Lancet* 2000

SSRI/SNRI dosing for PMDD

Treatments proven effective[1]

1. **Continuous dosing**
   - Daily use throughout the menstrual cycle
   - Treats both psychological and physical symptoms of PMDD[1]
2. **Intermittent/luteal-phase dosing**
   - 14 days prior to menses until cycle day

What about symptom-onset dosing?

Small studies (N <30) suggest benefit

- Luteal phase and symptom-onset dosing of escitalopram (average 6 days) equivalent over 3 cycles[3]
- Women with more severe symptoms less likely to respond to symptom-onset dosing[3]
- Symptom-onset paroxetine CR (average 9 days) superior to placebo in crossover trial[4]

[1] Cochrane Database Syst Rev 2002; [2] Steiner M, et al. *Br J OBGYN* 2001;
[3] Freeman EW, et al. *J Clin Psychiatry* 2005; [4] Yonkers KA, et al. *J Clin Psychopharmacol* 2006

Consideration in selecting SSRI vs. HC for PMDD treatment

SSRI

- Advantages
  - Extensive investigation with multiple trials showing efficacy
  - Continuous and intermittent dosing options
  - 3 FDA-approved agents (fluoxetine, sertraline, and paroxetine CR)
  - Treat concurrent depression and/or reduce the risk of depression recurrence
- Disadvantages
  - Pregnancy during treatment
  - Potential long-term adverse effects of weight gain and sexual dysfunction

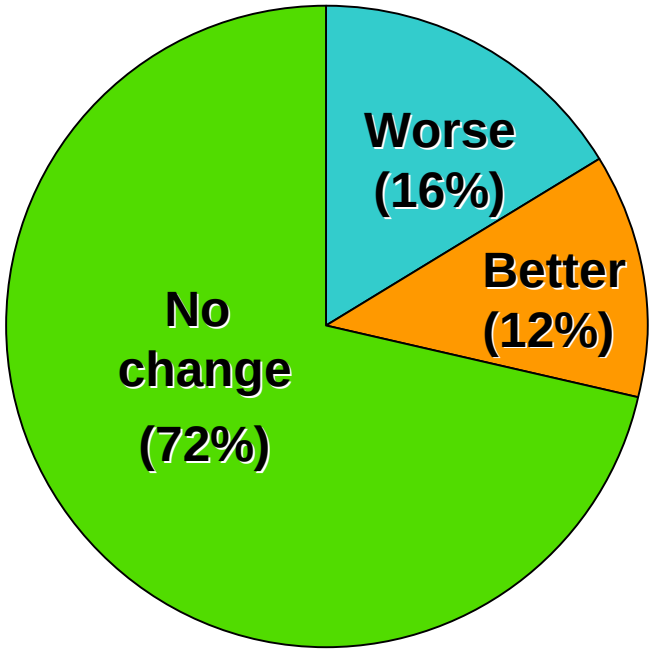
HC = hormonal contraceptives

Hormonal contraceptive pills

- Advantages
  - Concurrent benefits
    - Contraception
    - Acne treatment
    - Reduced menstrual flow
  - Long-cycle treatments
- Disadvantages
  - Less extensive study
  - HC side effects and risks
  - Smoking contraindication >35 years old
  - Rare mood side effects

Impact of oral contraceptives on premenstrual mood

- Epidemiologic study of 658 women 36–45 years, who previously used a variety of OC preparations
- OC's do not affect premenstrual mood in the majority of women
- History of depression is strongest predictor of worse mood on OC
  - But only 25% of women with depression histories had mood worsening on OC
  - 61% had no change in mood
  - 14% experienced improvement in mood



OC = oral contraceptives

Joffe H, et al. *Am J Obstet Gynecol* 2003

Hormonal contraceptives and long-term risk of depression

Systemic hormonal contraceptives

Estrogen + progestin

Progestin only

Local (IUD)

Table 2. Rate Ratio of First Use of Antidepressants and First Diagnosis of Depression in All Women[a]

Type of Hormonal Contraception	Person-years	First Use of Antidepressants			First Diagnosis of Depression		
		No. of Events	RR[b]	RR (95% CI)[c]	No. of Events	RR[b]	RR (95% CI)[c]
Nonuse	3 041 595	50 346	1	1 [Reference]	9310	1	1 [Reference]
All oral combined	3 518 381	74 126	1.2[d]	1.2 (1.22-1.25)[d]	12 211	1.0[d]	1.1 (1.08-1.14)[d]
All progestin-only	74 540	1884	1.3[d]	1.3 (1.27-1.40)[d]	296	1.1	1.2 (1.04-1.31)[d]
Nonoral							
Levonorgestrel IUS	81 281	2373	1.4[d]	1.4 (1.31-1.42)[d]	397	1.4[d]	1.4 (1.22-1.50)[d]

Abbreviations: IUS, intrauterine system; RR, incidence rate ratio.

[a] Includes 1 061 997 women aged 15 to 34 years.

[b] Adjusted for age and calendar year.

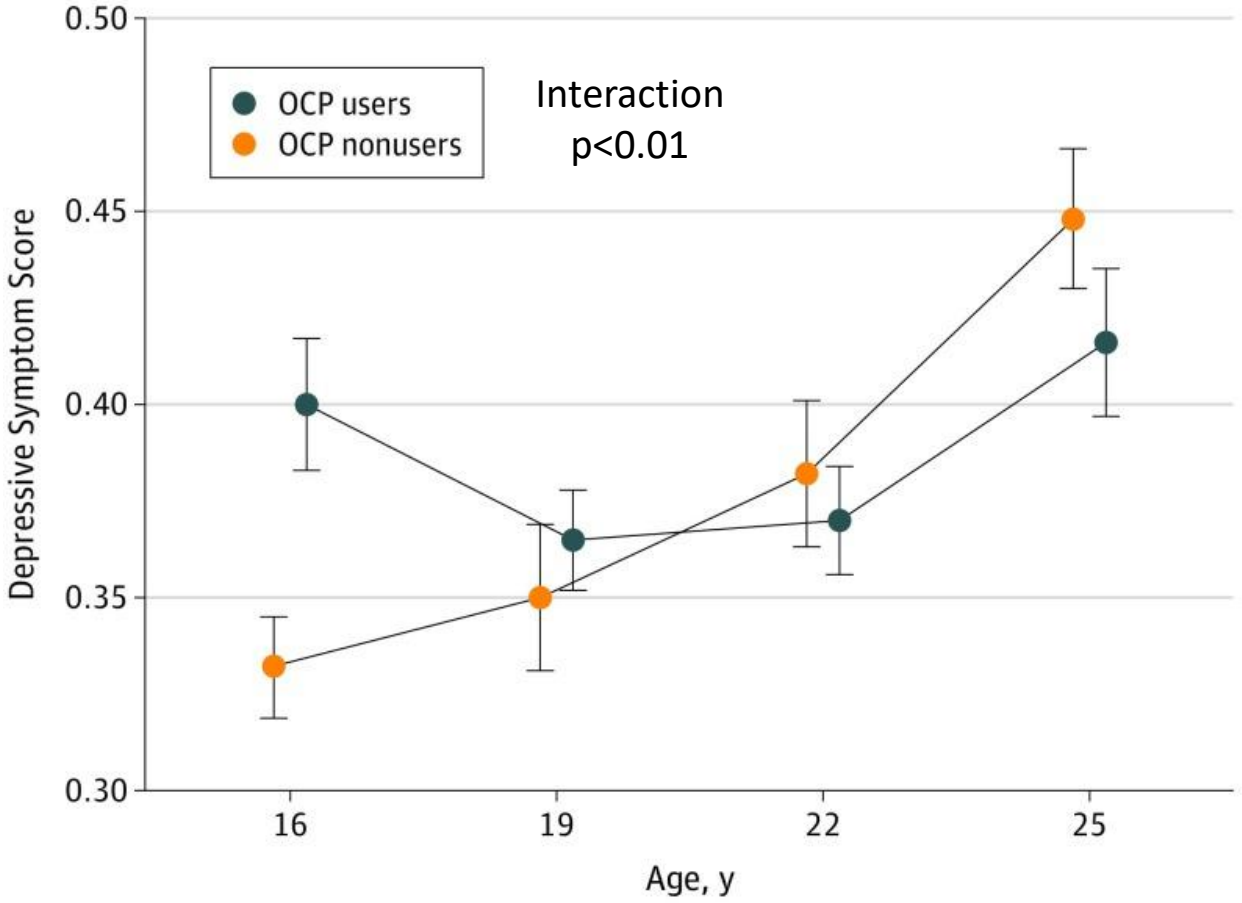
[c] Adjusted for age, calendar year, educational level, polycystic ovary syndrome, and endometrioses.

[d] Indicates statistical significance.

- Risk of antidepressant use and of depression diagnosis is years later
- HC use in teens associated with greater risk of subsequent depression

et al. *JAMA Psychiatry* 2016

Hormonal contraceptives and risk of concurrent depressive symptoms by age



Use in teens associated with risk of **concurrent** depressive symptoms

OCP = oral contraceptives pills

De Wit, et al. *JAMA Psychiatry* 2021

"My PMS is so bad that it lasts all month long"

Premenstrual worsening of mood disorder

- 64% of women with major depression not taking an HC report premenstrual worsening of depression[1]
- Ask about mood symptoms in the follicular phase
- Prospectively document temporal relationship between mood symptoms and menses
- Don’t miss underlying mood disorder
  - Continuous versus luteal-phase SSRI therapy
- Treatment: HC augmentation may not be effective [2]

HC = hormonal contraceptives

[1] Kornstein SG, et al. *Psychol Med* 2005; [2] Peters W, et al. *J Clin Psychopharm* 2017

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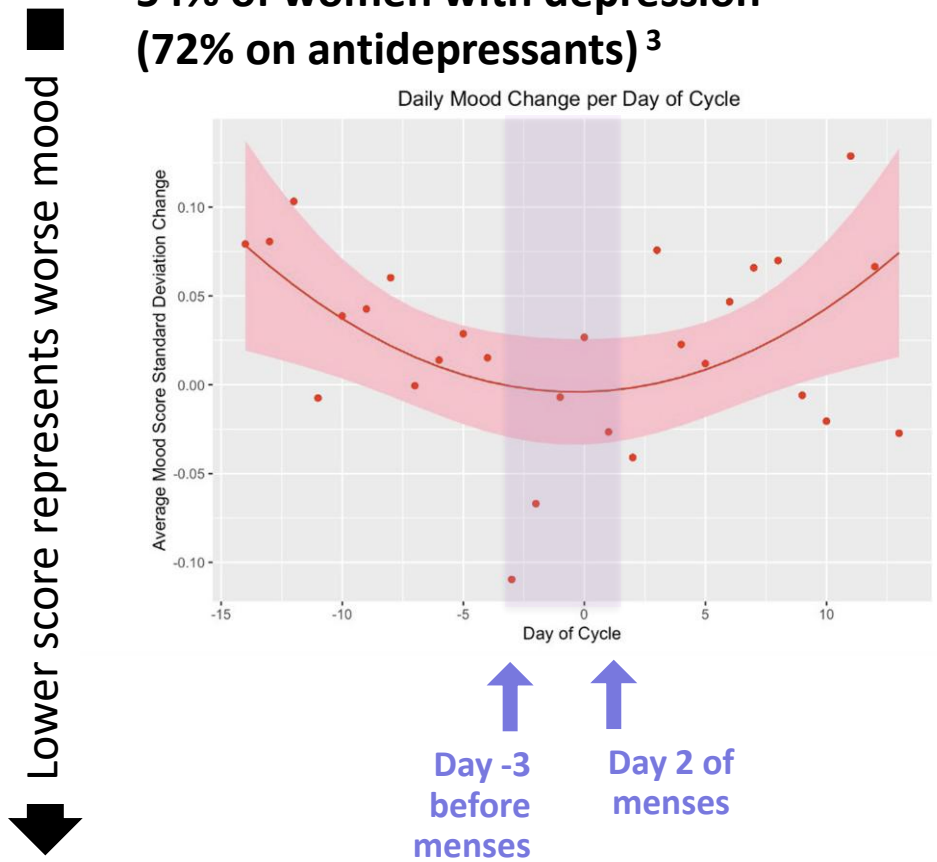
HC = hormonal contraceptives

Mood worsens surrounding menses in 54% of women with depression (72% on antidepressants) [3]



[1] Kornstein SG, et al. *Psychol Med* 2005; [2] Delray K, et al. *BMJ Mental Health* 2017; [3] Peters W, et al. *J Clin Psychopharm* 2017

Summary: PMDD, premenstrual exacerbation of depression, and use of hormonal contraceptives

1. **PMDD is severe menstrually-linked, hormonally-based mood-dominant form of PMS with adverse impact of function**
   - **Can be treated with systemic hormonal contraceptives or serotonergic antidepressants**

2. **Premenstrual exacerbation of depression is common**

3. **Hormonal contraceptives have concurrent and long-term risks of depression**
   - **May not be biologically driven risk**
   - **Hormonal contraceptives should not be withheld from individuals with depression**

It takes a village……

WOMEN'S HORMONES AND AGING RESEARCH PROGRAM

Sleep Medicine

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Endocrinology / GYN

Aviva Cohn, MD, Janet Hall, MD, Ursula Kaiser, MD, Caroline Mitchell, MD, Victor Navarro, PhD, Jan Shifren, MD

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