Reproductive Psychiatry: 2020 Update

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OHSU Center for Women's Health
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Is this the year for neurosteroids?

- What is a neurosteroid?
- First ever sex specific treatment for “depression” - Brexanolone

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Pharmacologic treatment in Women - 2020

SSRIs or SNRIs

- Moderate to severe depression or anxiety
- Most effective if in combination with psychotherapy

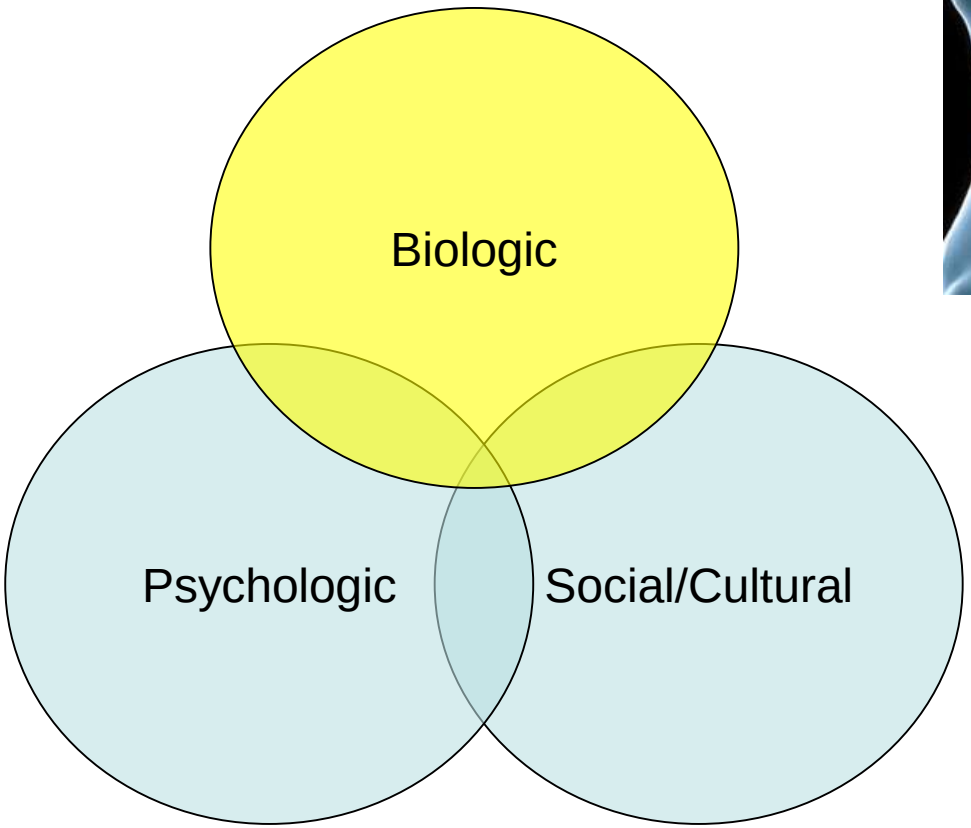
- Effect in 2-6 weeks

vs. Neurosteroids

- Allopreg. In PPD
- Mild depression or anxiety if other symptoms present **during perimenopause**
- New onset depression during **perimenopause**
- In combination with SSRIs for severe depression **perimenopause and menopause**
- If comorbid hot flashes present and do not have MDD
- Surgically induced menopause
- Testosterone for Low Libido
- Oxytocin for BPD or Autism?
- Tamoxifen for Bipolar disorder

- Effect in 2-4 weeks

Male/Female Brain Differences



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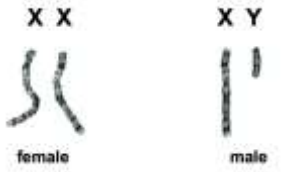
Why does sex* matter in psychiatric illness?

- Every cell has a sex
  XX or XY chromosome



- Sex influences fundamental biology hormones, X dose, Y dose, female mosaicism, parental X imprinting
- Sex affects sexual behavior, neuro behavior, aging, expression of illness, etc.
- Novel therapies
  - Dissections of mechanisms that protect one sex can be harnessed to treat both sexes
  - e.g. Anxiety disorders, Alzheimer's

*Sex is defined by biologic differences between males and females based on genetics.
Gender is more loosely defined – social cultural influences, identification and role in society.

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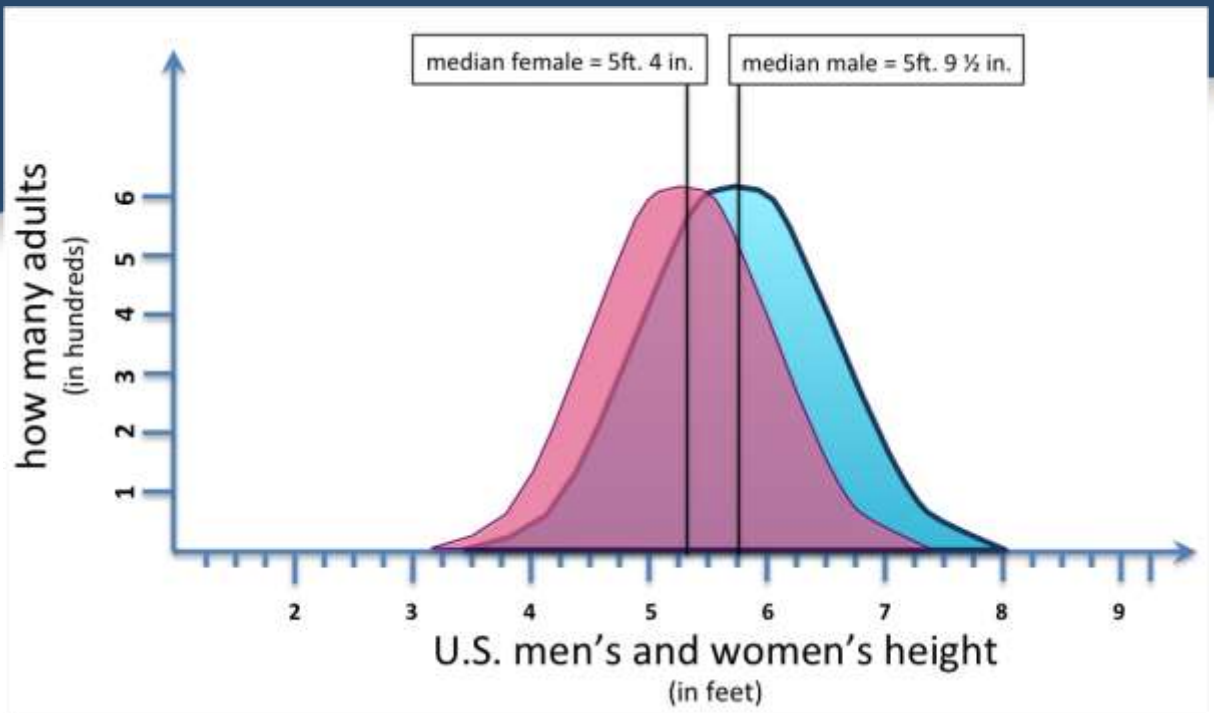

Estrogen – Brain effects

- Facilitates gender specific behaviors in women
  - Interpersonal aptitude
  - Verbal Agility
- Inhibits Fear Response
- Likely contributes to increased depression and anxiety rates

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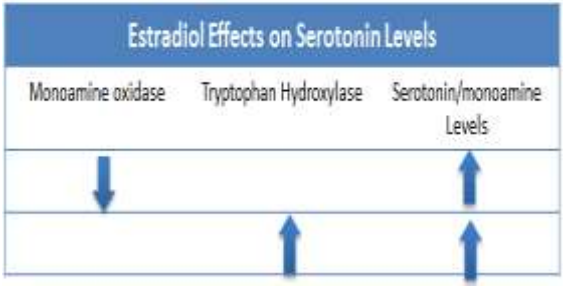
Estrogen – Mood Enhancing Effects

- Estrogen supports Serotonin
  - Increases synthesis (tryptophan)
  - Increased 5HT1 receptors in Dorsal Raphe
  - Reduces metabolism of serotonin (Decrease MAO activity)
- Estrogen supports Norepinephrine
- Antidopaminergic effects



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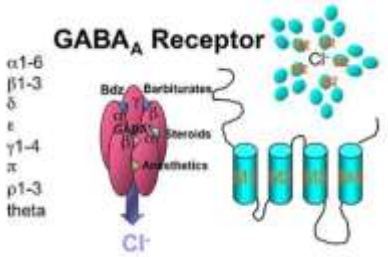
Progesterone – Anti anxiety effects?

- Elevated in pregnancy with rapid drop postpartum
- Fluctuates monthly –withdrawal premenstrually
- Significant decline in menopause
- Progesterone targets areas of the brain **similar to anti-anxiety, pain and sleep medications**
- Clinical studies show it has **hypnotic and anxiolytic** as well as **dysphoric** effects in postmenopausal women



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Oxytocin (OT) and Attachment

- Fosters attachment b/w all mammalian mothers and infants
- Improves ability to interpret social situations and facilitates attending to others
- OT activates limbic structures assoc. with emotion and *attention*
- Postpartum women: Lactation suppresses physiologic response to stress.
- Lactation decreases anxiety symptoms vs. PP controls.
- Promotes amnesia during labor

Oxytocin in men

- Improves social reciprocity in men
- Improves the ability to identify competitive relationships
- Fosters striving to improve social status
- Improves males perception of desirability in their mate

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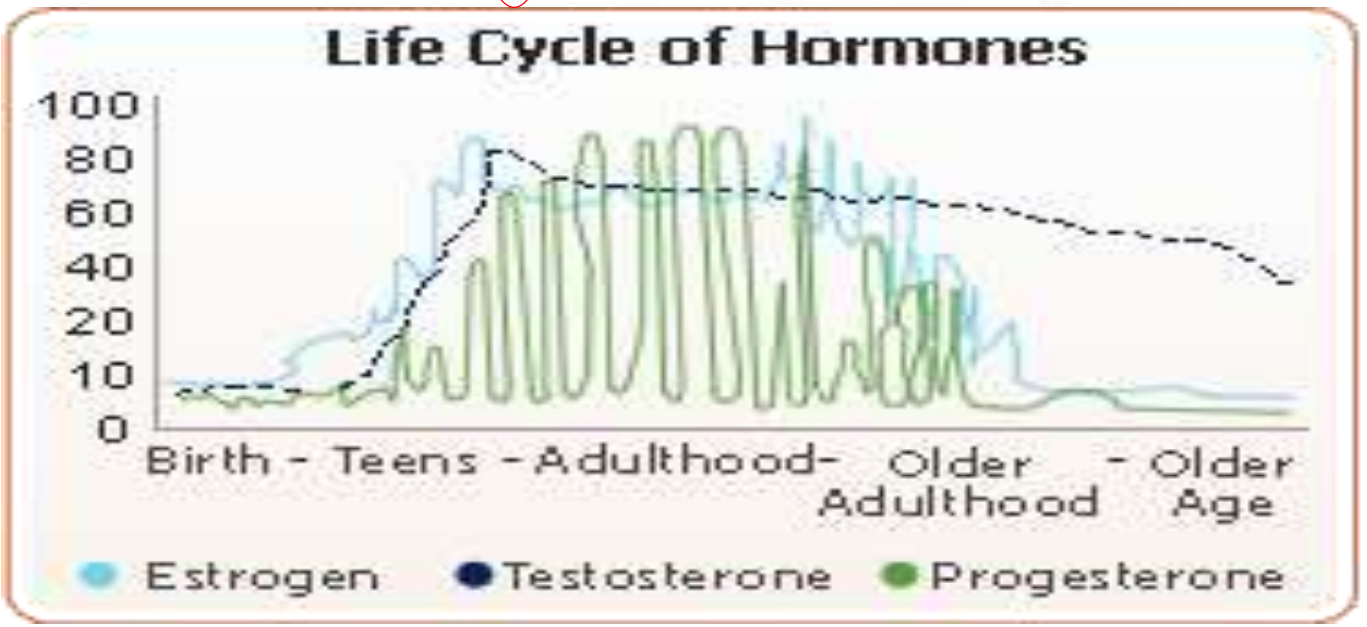
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Birth - Teens - Adulthood- Older Adulthood - Older Age
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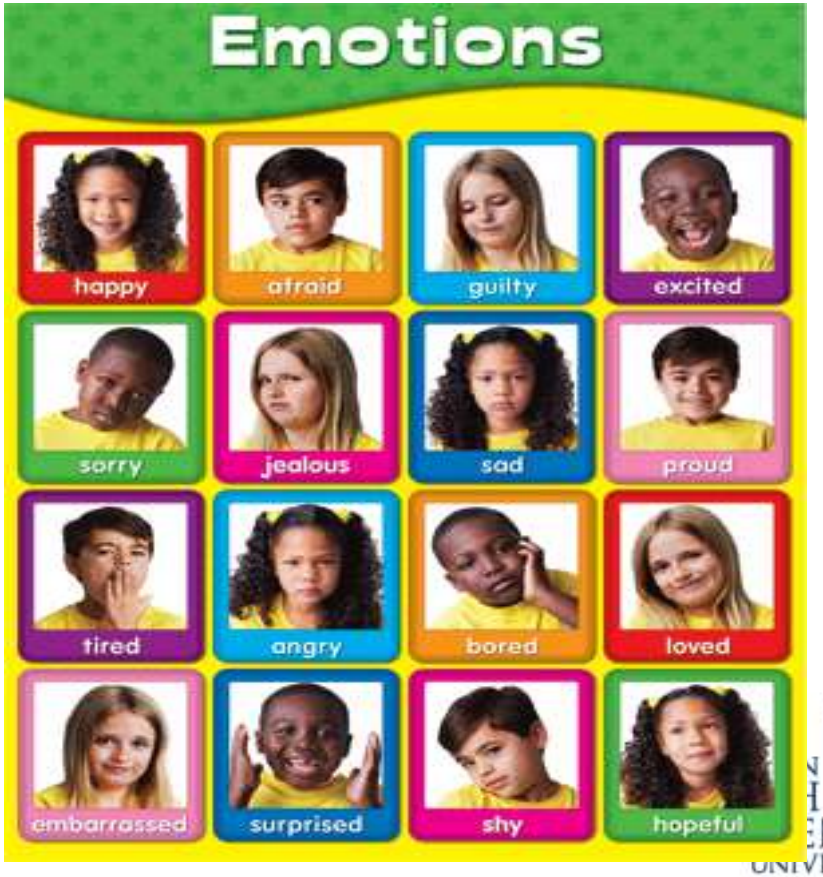
Testosterone
Progesterone

Brain changes -School Age girls

Total speech



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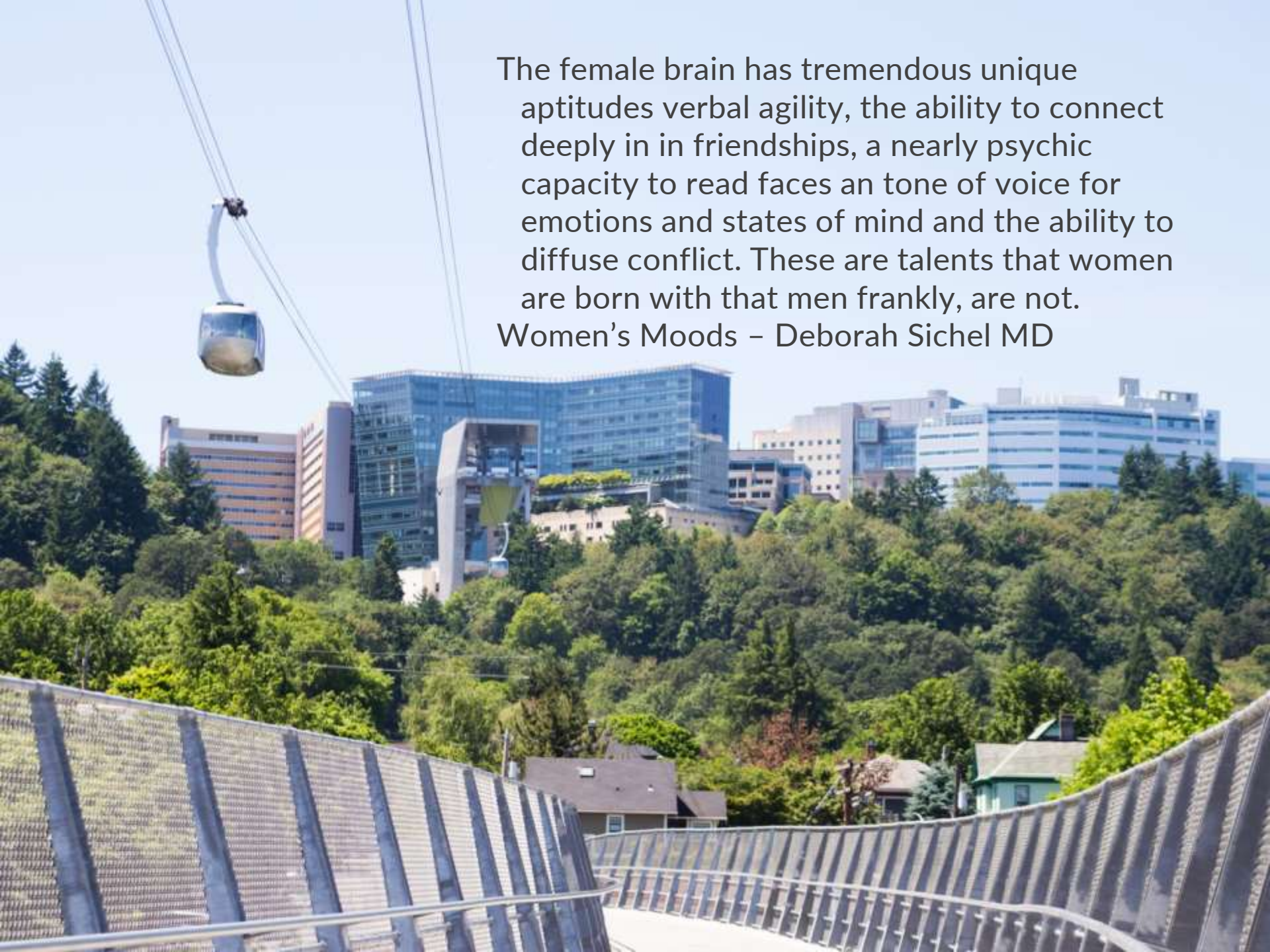
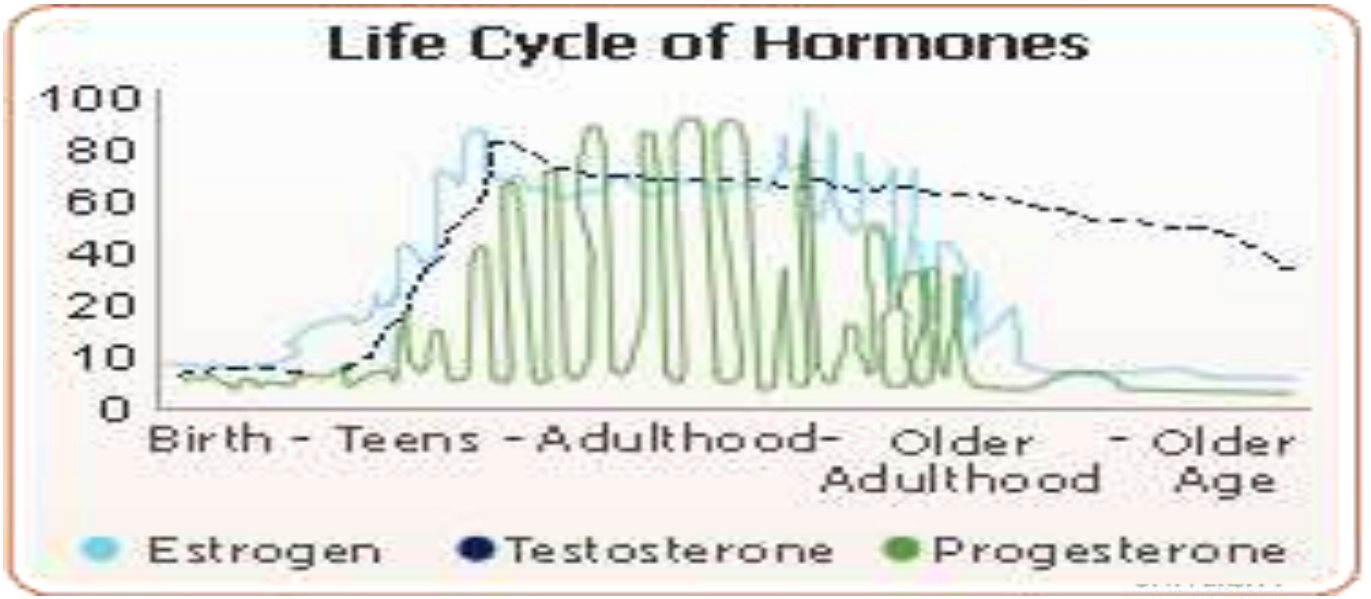


The female brain has tremendous unique aptitudes verbal agility, the ability to connect deeply in in friendships, a nearly psychic capacity to read faces an tone of voice for emotions and states of mind and the ability to diffuse conflict. These are talents that women are born with that men frankly, are not.

Women's Moods – Deborah Sichel MD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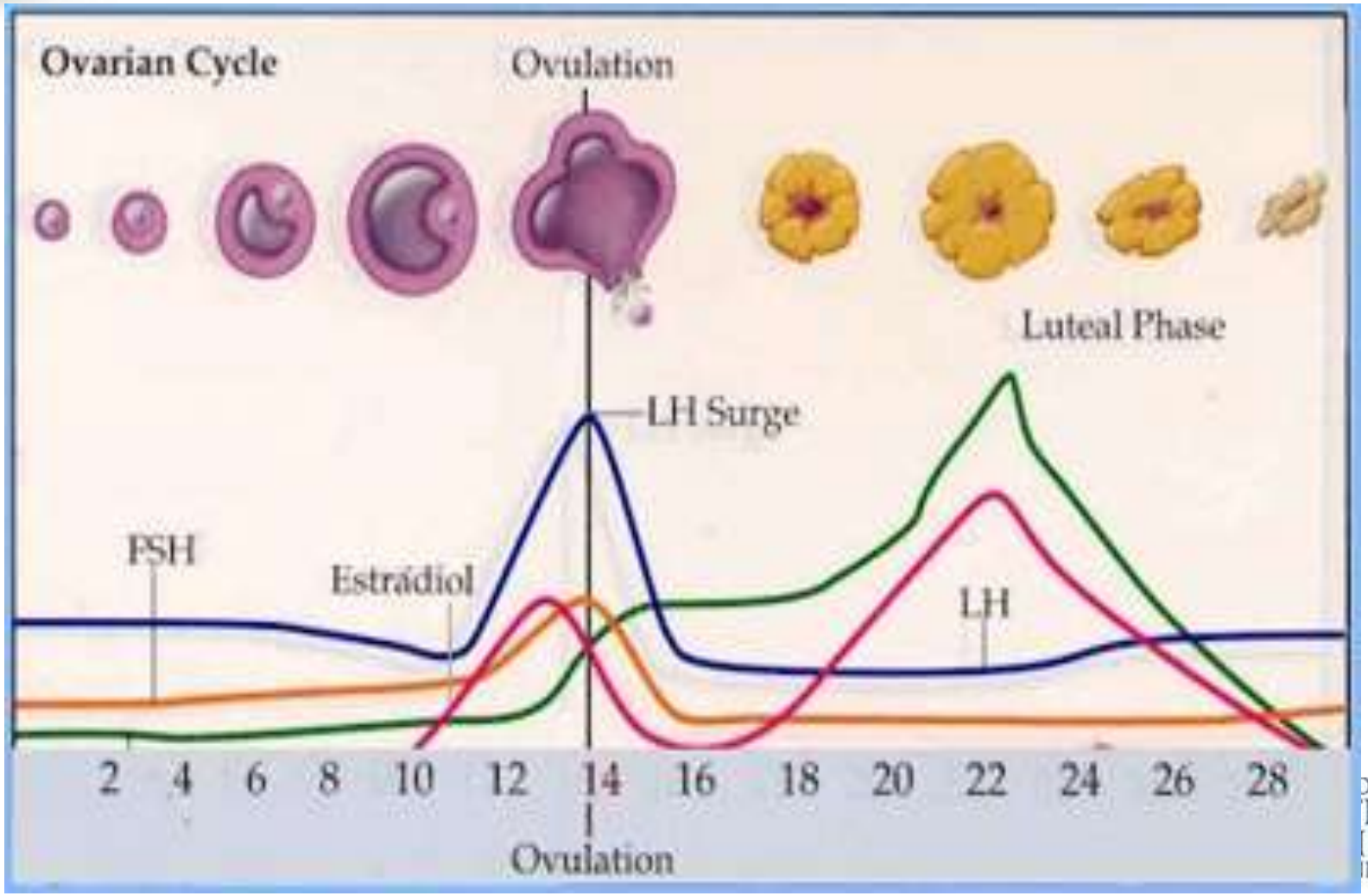
Brain Changes – Puberty (Menses begins)



Depression Rates by Gender

Age Group	Female	Male
14-16y/o	13.3%	2.7%
18-24y/o	6.9%	3.8%
25-44y/o	10.8%	4.8%
45-64y/o	7.8%	3.3%

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Expression of Psychiatric Illness by Gender

More common in Males	More common in Females
Antisocial Personality Disorder/ Behavior	Depressive Disorders
Autism	Anxiety Disorders
Schizophrenia	Bipolar II disorder
Addiction	
Schizophrenia	

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Anxiety Rates by Gender

	Female	Male
Panic Disorder	5.0%	2.0%
Agoraphobia	7.0 %	3.5%
PTSD	10.4%	5.0%
GAD (Generalized Anx. Dis)	6.6%	3.6%
SAD (Social Anx. Dis)	15.5%	11.1%
OCD (Obsessive Compulsive Dis)	3.1%	2.0%

Antidepressants in Women

- Plasma levels tend to be higher in women; usually not clinically significant
- “Hyperstimulation” side effect more common in women
- Women take more psychotropic medication
- Women are twice as likely as men to report side effects
- Women take more multiple medications

Premenstrual Effects of Pharmacokinetics

- GI transit time slower
- Plasma volume increases enough to dilute water soluble drugs
- Estrogen induces liver enzymes, increases catabolism premenstrually
- Overall effect: serum levels are less predictable, usually lower if changed

Premenstrual symptom patterns

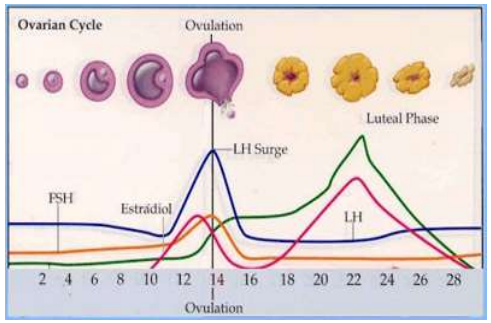
- PMS: mild premenstrual symptoms, not constituting a disorder (30-80% women)
- PMDD: SX severe enough to cause impairment (3-5%)
- PME: A primary psychiatric disorder that becomes activated premenstrually (e.g 25-50% of women with depression)

PMDD

- Average age of onset is in late 20's
- PMDD correlates with higher risk of postpartum depression and perimenopausal depression
- Correlates with higher risk of seasonal affective disorder
- Higher concordance in monozygotic twins

Premenstrual Dysphoric Disorder- DSM-5 Symptoms

- Depressed mood
- Anxiety/tension
- Affective lability
- Anger/ irritability
- Anhedonia
- Concentration difficulties
- Energy
- Appetite
- Feeling overwhelmed
- Physical symptoms



- ✓ Five must occur in most cycles over past year
- ✓ Occur most of the time during the last week of the luteal phase
- ✓ Begin to remit during the follicular phase
- ✓ Absent in the week post menses
- ✓ Markedly interferes with work, school, social activities
- ✓ Confirmed in two consecutive monthly cycles

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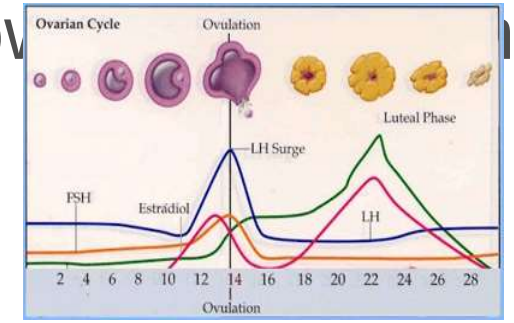
Biological basis of PMDD

- Levels of estrogen, progesterone and Gonadotropins are normal
- Serotonin (estrogen) and GABA agonist (progesterone) abnormalities present
- In luteal phase, Serotonin and Gaba levels do not rise in PMDD women versus controls
- Allopregnanolone is lov ptom severity is highest.



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Disorders With Premenstrual Exacerbation (PME)

- Dysthymic Disorder
- Major depression
- Panic Disorder
- Obsessive Compulsive Disorder
- Bipolar Mood Disorder (esp. rapid cycling)
- Schizophrenia

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Dosing strategies with SSRIs

- Fluoxetine less likely to have menstrual fluctuations, due to longer half life
- Fluoxetine, Sertraline, Citalopram with proven efficacy for PMDD

❑Continuous dosing

❑Luteal Phase Dosing (PMDD) 6-14 days prior to menses

❑Luteal phase boosting (PME)

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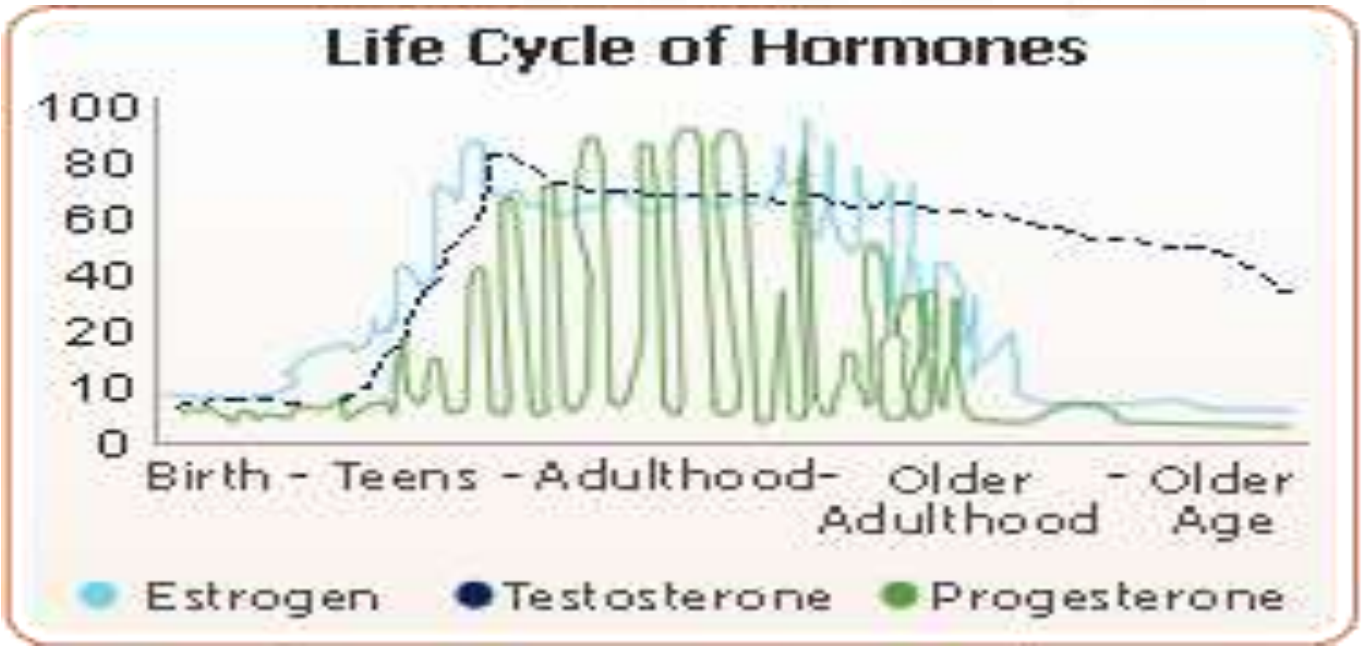
Pharmacologic Treatment of PMDD Cont.

- OCP's - mixed results
- Leuprolide – GNRH antagonist, suppresses ovulation.
- Danazol – (synthetic androgen)

  low doses in luteal phase may be helpful
- Add back techniques (Leuprolide plus Timolide)
- TAH/BSO (only if other indication is present)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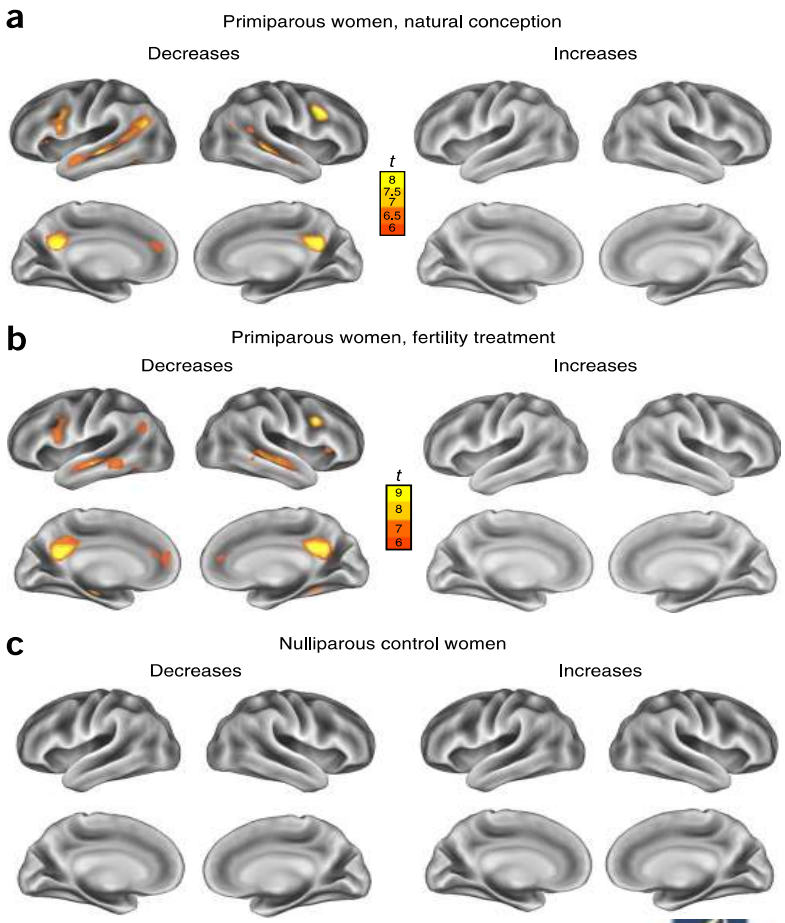
Perinatal Mood and Anxiety Disorders (PMADs)

g changes in human brain structure

Decrease in grey matter assoc. with social cognition

Pruning of glial cells and neurons

Maturation of brain function –fine tuning



Hoekzema et al Nature Neuroscience 2017

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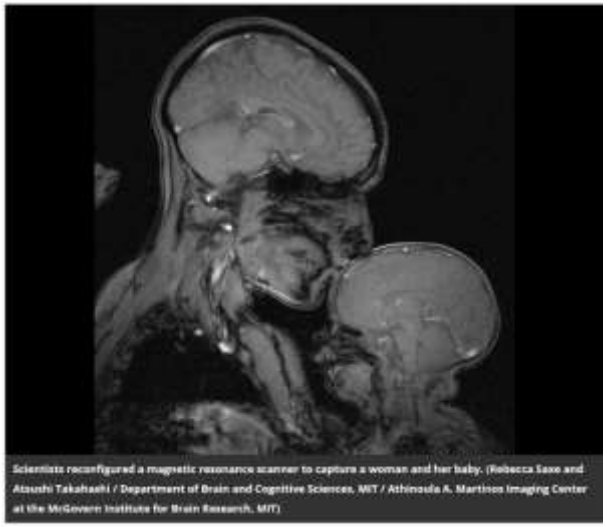
A “sensitive period” – Brain changes in motherhood

- Enable a mother to multitask to meet her babies needs
- Emphasize with the infants emotion and pain (and others)
- Decode social stimuli that may equal threat
- Sync her brain with her babies for life
  - Synchronized brain responses
  - Matching responses in gaze, touch and vocalization
- Neuronal plasticity that is also receptive to interventions



Elseline Hoekzema Leiden U, Netherlands 2016

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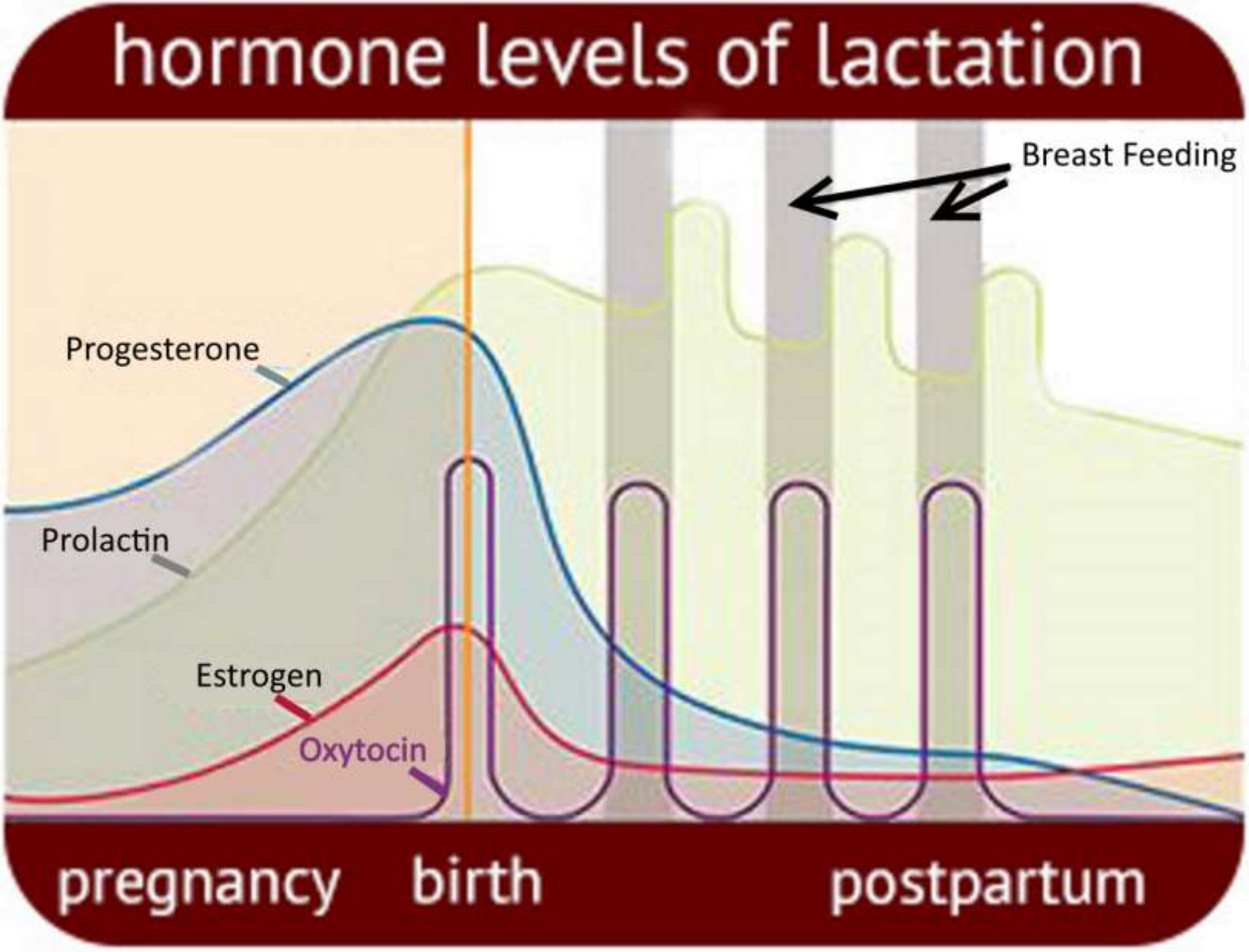
hormone levels of lactation
Breast Feeding
Progesterone
Prolactin
Estrogen
Oxytocin
pregnancy
birth
postpartum

TABLE 3

Summary of current knowledge of antidepressant use during pregnancy

Antidepressants likely DO NOT increase the risk of

- Birth defects
- Spontaneous abortion, stillbirth, or neonatal death
- Cognitive impairment or behavioral problems
- Autism

Antidepressants MIGHT increase the risk of

- Late preterm birth (although more likely because of effects of depression)
- Postpartum hemorrhage (although more likely because of other confounders)

Antidepressants likely DO increase the risk of

- Neonatal side effects, especially respiratory distress
- Neonatal persistent pulmonary hypertension of the newborn infant, although rare

Perinatal prescribing pearls

- Ask patients what antidepressant has worked for them in the past and start with this (exception is paroxetine in the 1st trimester).
- One medication at a higher dose is preferable to multiple medications.
- Tapering antidepressants before delivery does not decrease potential fetal risks but does increase risk of symptom relapse postpartum.
- Do not switch effective antidepressants after delivery in lactating women.

Adapted and used with permission from Laura Miller, MD.

Thorsness. Perinatal anxiety: diagnosis/management in the obstetric setting. Am J Obstet Gynecol 2018.

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Brexanolone 3/19 FDA approved

2012 Update

New medication for moderate to sever postpartum depression

- An allosteric modulator of GABA-A receptors
- 3 days inpatient IV infusion
- Remission of depression often within 24 hours up to 30 days
- SE: Sedation effects ranged from somnolence to loss of consciousness. All resolved within 60 minutes of infusion discontinuation.
- Breastfeeding –12 women/infant dyads. Relative infant dose 1-2%.

1. *Kanes SJ, et al. Hum Psychopharmacol. 2017 Mar;32(2))*
2. *1. Hoffmann E, Wald J, Colquhoun H. Evaluation of breast milk concentrations following brexanolone iv administration to healthy lactating women. Am J Obstet Gynecol. 2019;220:S554. Abstract. DOI: doi:10.1016/j.ajog.2018.11.873*
3. *Hoffmann E, Wald J, Dray D et al. Brexanolone injection administration to lactating women: Breast milk allopregnanolone levels. Obstet Gynecol. 2019;133 (Suppl 1):115S. Abstract 30J. doi:10.1097/01.AOG.0000558846.15461.70 DOI: doi:10.1097/01.AOG.0000558846.15461.70*

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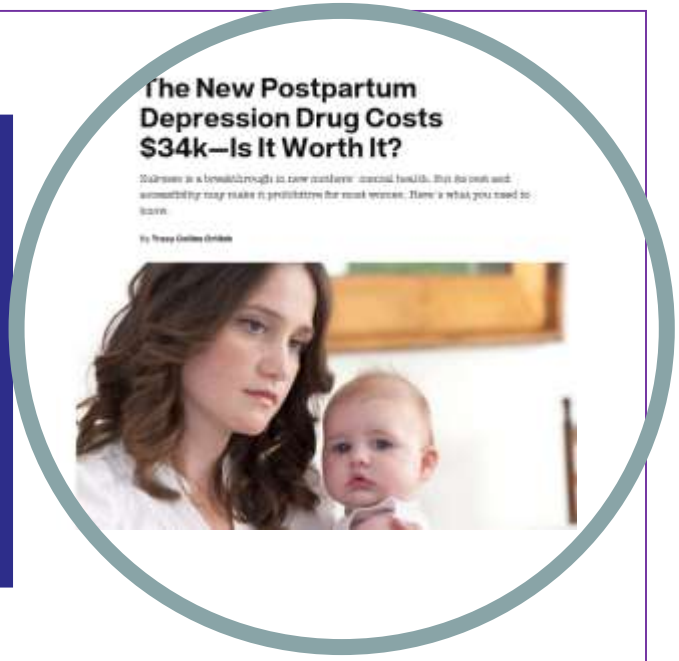
Brexanolone 1 year later - Barriers to care
Who, Where, How Much, When?

FDA requires REMS Registration



Who is the right patient for BRX?

DSM-IV or DSM-5

First Line? **Second Line?**

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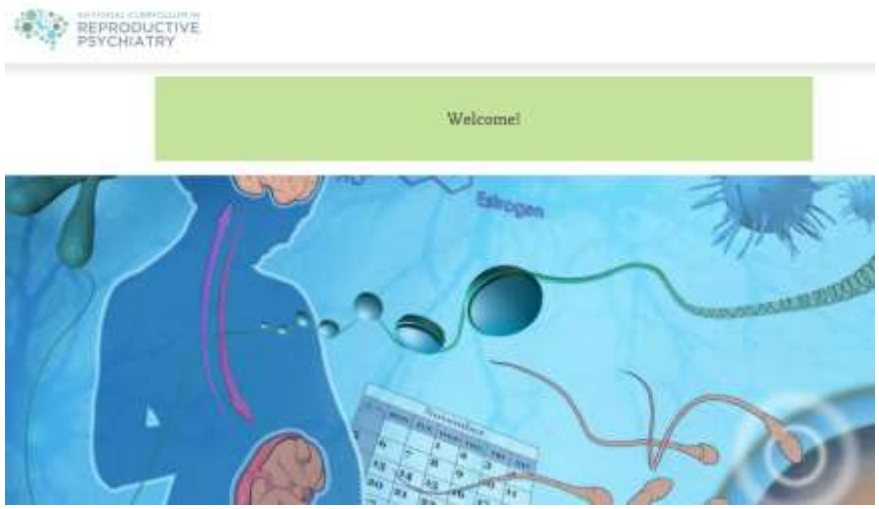
New in 2019!

National Curriculum in Reproductive Psychiatry

- 2019 FREE Course materials
- online at:
- **http://ncrptraining.org/**



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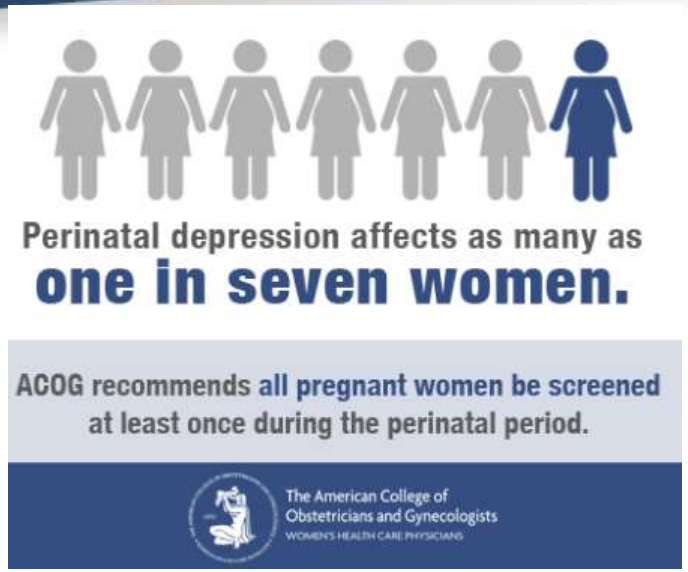
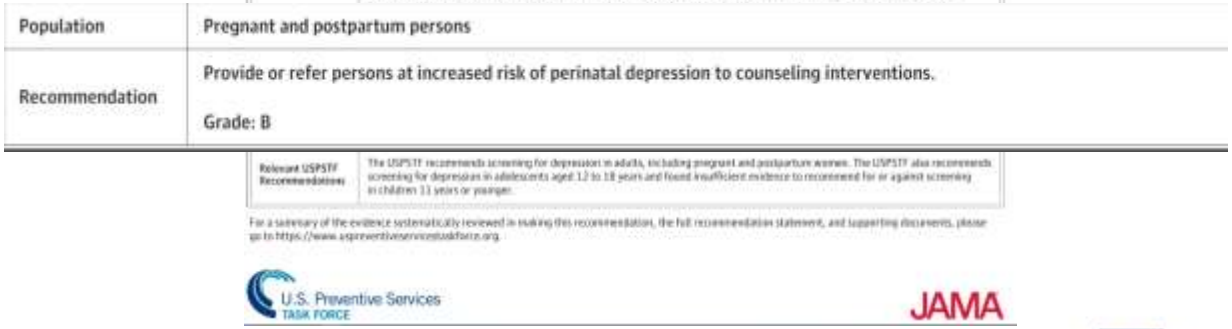
Policy Changes -2020 Update



The AAP recommends integrating postpartum depression surveillance and screening at the 1-, 2-, 4-, and 6-month visits.



JAMA. 2019;321(6):580-587

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2020-Reproductive Psychiatry Consult Lines(free)

Perinatal Psychiatric Consult Line

PSI Perinatal Psychiatric Consult Line
1-800-944-4773, ext 4

Medical Providers:

Fill Out This Form to request an appointment with one of our psychiatric consultants.

The PSI perinatal psychiatric consultation line is a service provided at no cost.

The consultation line is available for medical professionals who have questions about the mental health care related to pregnant and postpartum patients and pre-conception planning. This consultation service is available for medical providers only.

The Perinatal Psychiatric Consult Line is staffed by reproductive psychiatrists who are members of PSI and specialists in the treatment of perinatal mental health disorders. The service is free and available by appointment.

Call 800-944-4773, ext 4 and we will match you with an appointment. We will respond to your request within one business day.

Massachusetts General Hospital Postpartum Psychosis Project (MGHP3)

About Postpartum Psychosis | Resources | Survivor Stories | Case-Based Supervision

Case-Based Supervision for Providers

The MGH Postpartum Psychosis Project is pleased to announce that it will offer free "curbside case-based supervision" to providers caring for patients with acute postpartum psychosis, or those who are still suffering after an episode. Postpartum psychosis is a rare and understudied condition and we are happy to make ourselves available to providers by email and phone for brief discussions. Please read the FAQ below and submit a request to be connected with a member of our faculty. Please note that we are able to offer this service solely to care providers.

FAQ

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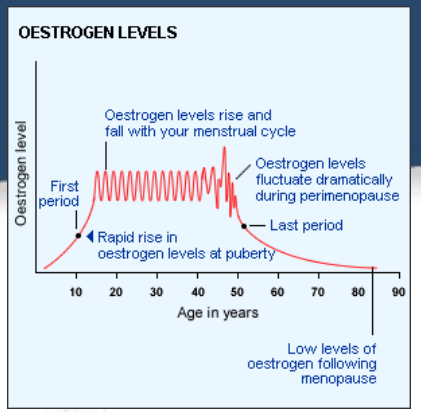
Menopause



- In 1900, average age of menopause=45
  - Life span = 49 years old
- Today, women experience menopause between 45-55
  - Average life span = 75 years
  - 20-30 years or more are post menopause

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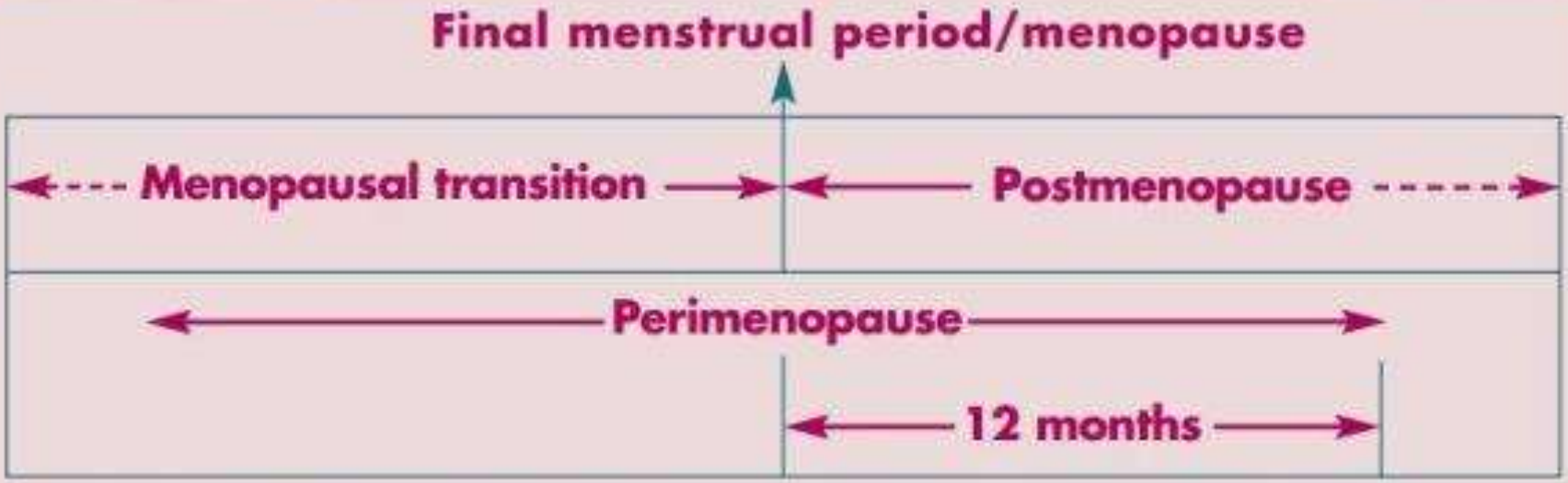
Menopause timeline



World Health Organization. Research on the menopause in the 1990s: report of WHO scientific group. Geneva: WHO Technical Series 866; 1996; page 13.

FSH> 30
Estradiol <200

Reference Intervals	FSH (IU/L)	LH (IU/L)	Oestradiol (pmol/L)	Progesterone (nmol/L)
Female:				
Follicular phase	2.8 - 9.3	2.8 - 7.6	46 - 607	0.6 - 4.7
Mid cycle	3.0 - 19.2	10.5 - 85	315 - 1828	2.4 - 9.4
Luteal phase (D21)	1.7 - 7.7	1.0 - 11.4	161 - 774	5.3 - 86
Postmenopausal	31 - 153	12.0 - 75	<200	0.3 - 2.5

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PERI
MENOPAUSE
AHEAD

2018

First-ever guidelines for detecting, treating perimenopausal depression

by University of Illinois at Chicago

Menopause: The Journal of The North American Menopause Society
Vol. 25, No. 10, pp. 000-000
DOI: 10.1097/GME.0000000000001174
This article is being co-published in the journals *Journal of Women's Health* and *Menopause*

CONSENSUS RECOMMENDATIONS

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*

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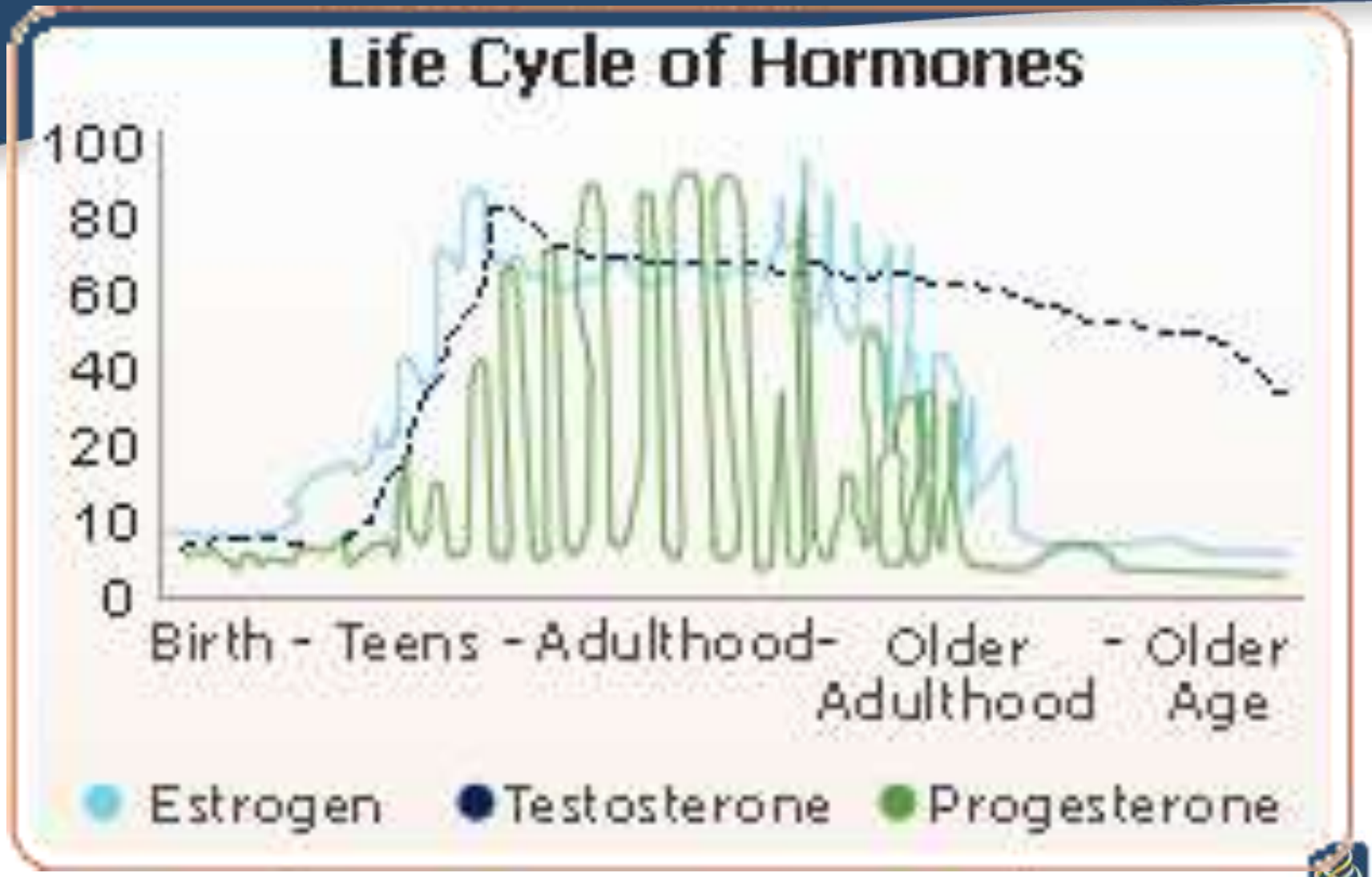
Co occurring symptoms

Depression

✓	SIGNS AND SYMPTOMS OF DEPRESSION
	Sadness or an "empty" mood
	Feeling guilty, worthless, or helpless
	Problems concentrating, remembering, or making decisions
	Change in eating habits and/or weight changes
	Feeling hopeless
	Lack of energy or feeling tried and "slowed down"
	Problems with sleep: Trouble getting to sleep, staying asleep, or sleeping too much
	Easily angered or irritable
	Wanting to be alone or spending much time alone
	Loss of interest or pleasure in hobbies and activities, including sex, that were once enjoyed

Perimenopause

- VMS
- Sleep disturbance
- and sexual disturbance
- Weight and Energy changes
- Cognitive shifts
- Urinary symptoms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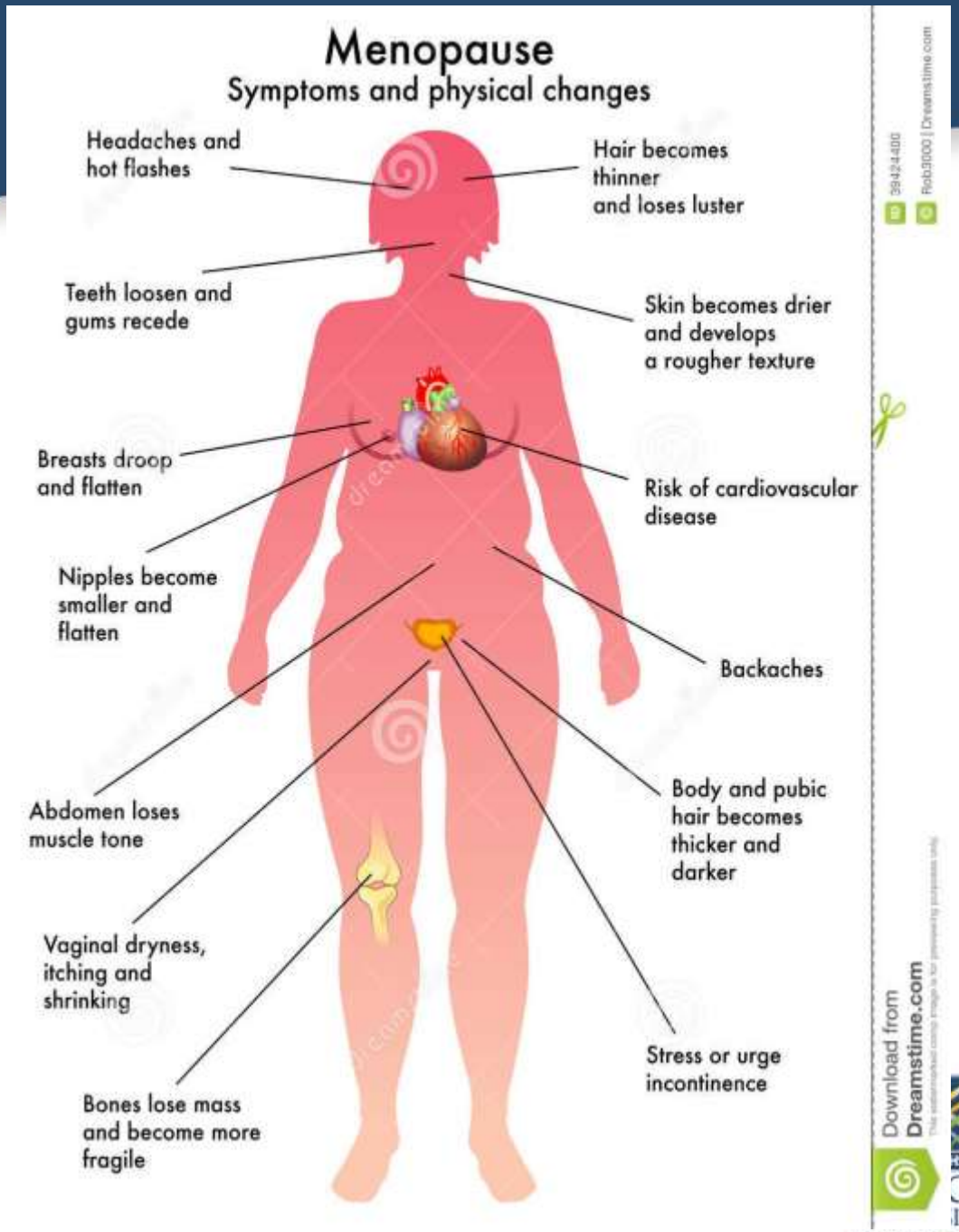
Progesterone

Panic disorder/Generalized Anxiety Disorder (GAD)

- New onset Panic Disorder and Generalized Anxiety Disorder more common during perimenopause
- More common in women with more physical symptoms of menopause (particularly Vasomotor symptoms)

Change in Physical Appearance

- Increase eating disorders
- Negative body image



Medication treatment for Depression

SSRIs or SNRIs

- Moderate to severe depression or anxiety
- History of depression
- Most effective if in combination with psychotherapy
- Start low and go slow, warn of SE of sweating, insomnia
- May also need to treat sleep

- Effect in 2-6 weeks

vs. Hormone therapy (Estrogen)

- Mild depression or anxiety if other symptoms present **during perimenopause**
- New onset depression during **perimenopause**
- In combination with SSRIs for severe depression **perimenopause and menopause**
- If comorbid hot flashes present and do not have MDD
- Surgically induced menopause

- Effect in 2-4 weeks

Estrogen (ET) as treatment for midlife Depression?

NAMS Depression Guideline 2018 Menopause 25 (10) 2018)

- ET is shown to be effective in depressed perimenopausal women c/ or c/o VMS
- ET enhances mood and improves well-being in non depressed peri- women
- OCPs (continuous) help with PMI
- There may be some benefit for ET for prevention of depression in peri-women

- ET is not effective in postmenopausal women
- ET is not FDA approved to treat depression in women of any age
- ET is CI in women with a hx of Estrogen positive CA

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Evidence insufficient for treatment of MDD during perimenopause

Table 5. Biologically Based Therapies That are Potentially Helpful in Patients With Premenstrual and Perimenopausal Mood and Anxiety Symptoms ⇦

Supplement	Evidence
Black cohosh (for hot flushes)	One RCT with positive evidence; six with negative evidence
Calcium (600 mg twice per day)	Two RCTs with positive evidence
Chasteberry (*Vitex agnus castus* fruit extract)	Eight RCTs with positive evidence, two with negative evidence
Evening primrose oil	Two RCTs with negative evidence
Ginkgo biloba	One RCT with positive evidence
Magnesium (400 mg/d)	Two RCTs using magnesium oxide with negative evidence, one RCT using magnesium pyrrolidone carboxylic acid with positive evidence
St. John's wort	Two RCTs with negative evidence
Vitamin B_6 (50–100 mg/d)	Six RCTs with negative evidence; six RCTs with positive evidence
Vitamin E (400 international units per day)	One RCT with negative evidence; one RCT with positive evidence

Abbreviation: RCT, randomized controlled trial.

Data from Dante G, Facchinetti F. Herbal treatments for alleviating premenstrual symptoms: a systematic review. J Psychosom Obstet Gynaecol 2011;32:42–51; Whelan AM, Jurgens TM, Naylor H. Herbs, vitamins and minerals in the treatment of premenstrual syndrome: a systematic review. Can J Clin Pharmacol 2009;16:e407–29; van Die MD, Burger HG, Teede HJ, Bone KM. Vitex agnus-castus extracts for female reproductive disorders: a systematic review of clinical trials. Planta Med 2013;79:562-75; *and* Ismail R, Taylor-Swanson L, Thomas A, Schnall JG, Cray L, Mitchell ES, et al. Effects of herbal preparations on symptom clusters during the menopausal transition. Climacteric 2015;18:11–28.

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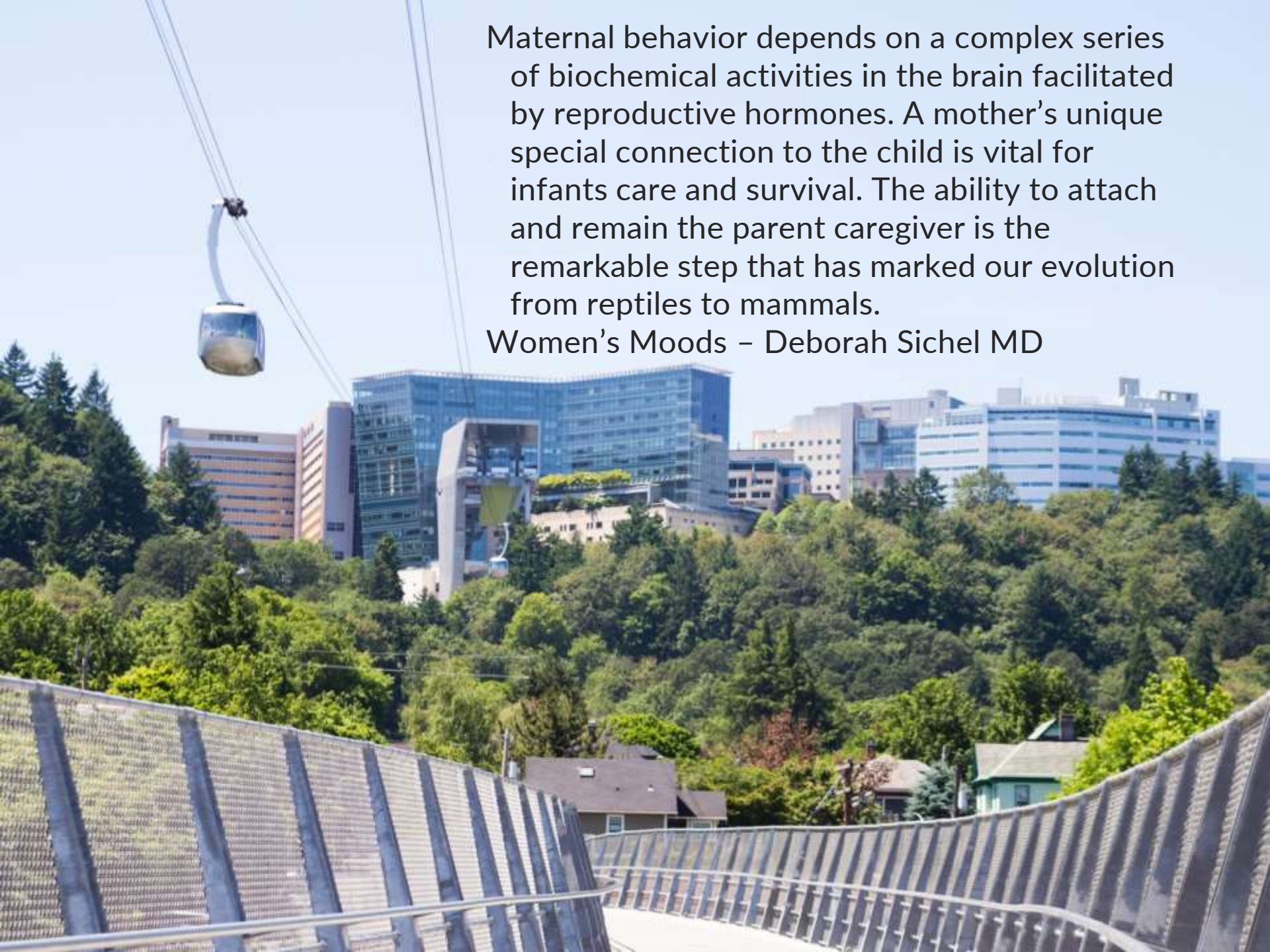

Maternal behavior depends on a complex series of biochemical activities in the brain facilitated by reproductive hormones. A mother's unique special connection to the child is vital for infants care and survival. The ability to attach and remain the parent caregiver is the remarkable step that has marked our evolution from reptiles to mammals.

Women's Moods – Deborah Sichel MD

Prescribing Pearls – Perimenopausal and Menopausal Depression

- Estrogen is ineffective in **post**menopausal depression
- Estrogen has been shown to enhance mood and improve wellbeing in non depressed **perimenopausal** women
- Hormonal contraceptives (continuous) have some data to suggest they improve mood regulation and depressive symptoms in perimenopause
- **Estrogen is not FDA approved to treat mood disturbance**

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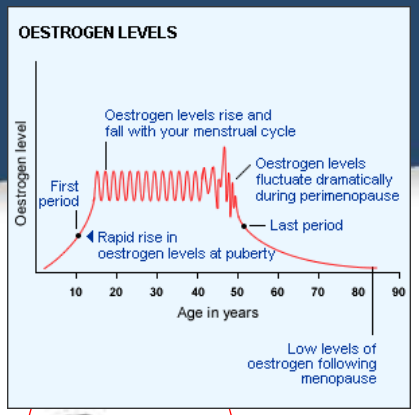
Post- menopause



- In 1900, average age of menopause=45
  - Life span = 49 years old
- Today, women experience menopause between 45-55
  - Average life span = 75 years
  - 20-30 years or more are post menopause

Estrogen and Dementia

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