U.S. Department of Veterans Affairs

Depression in Women

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DISCLOSURES

- No conflicts of interest
- No discussion of non-FDA approved medications or devices

PUBLIC HEALTH IMPACT OF MAJOR DEPRESSION

- 26% lifetime prevalence in women; 15% in men
- World Health Organization – leading cause of disability worldwide
- $210 billion per year cost in US
- Suicide
- Medical complications
- Adverse effect on pregnancy and offspring
- 35% no treatment

  National Epidemiologic Survey on Alcohol and Related Conditions III (NESARC-III) JAMA 2017.
- 42% of OEF/OIF Veterans who use VA care meet diagnostic criteria for depression following separation from military duty Seal et al., 2010

TOPICS

- Gender differences in depression
- Medical risk factors
- Menstrual cycle, fertility and contraception
- Pregnancy and the postpartum period
- Menopause
- Evaluation and treatment considerations

GENDER DIFFERENCES - PREVALENCE

- Women have higher rates of major depression
  also panic, PTSD, social phobia, generalized anxiety disorder

  Kessler et al., 1995, Weissman et al., 1994, Gater et al., 1998

- Women have higher rates of subclinical anxiety and depression

  Nolen-Hoeksema et al., 1999, Hankin, 2009

- Women use more internalized coping strategies (rumination); men use more action and distraction Gomez-Baya et al., 2017; Alloy et al., 2016

- Increased prevalence of depression in women begins at puberty, but increased risk of social anxiety, separation anxiety and phobias arise in childhood Salk et al, 2017

GENDER DIFFERENCES - SYMPTOMS

Depressed women more often experience

- increased appetite and hypersomnia
- gastrointestinal symptoms
- interpersonal sensitivity
- anxiety

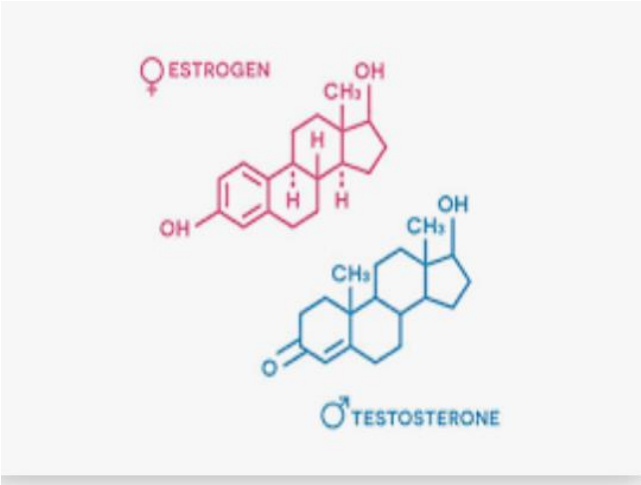
Women with bipolar disorder more often experience

- rapid cycling
- depression
- mixed episodes

GENDER DIFFERENCES - MECHANISMS

- Reproductive steroids are necessary for reproduction. They enable sperm and egg production, conception, pregnancy and lactation.
- Steroid hormones readily enter the brain and other body tissues, with wide-ranging effects.
- Some sex differences in brain structure and function may have evolved to make the effects of estrogen in women and testosterone in men more similar. Examples are parental behavior and hormonal responses to stress.

DeVries G, 2004



GENDER DIFFERENCES - MECHANISMS

• Some sex differences that promote reproductive success also likely increase vulnerability of women to mood and anxiety disorders.

• For example, adaptive behavioral differences in terms of childrearing seem to include, in females, superior social cognition and capacity for attunement with others, important for cognitive and social development of offspring

Halpern, 2007; Gur et al., 2012;Thompson and Voyer, 2014.

• However, these sex differences are also thought to result in women experiencing more sensitivity to rejection, criticism and separation, key features of depression and anxiety disorders

Cyranowski et al., 2000; Taylor et al., 2000; Zahn-Waxler et al., 2008, Martel, 2013

DEPRESSION - ETIOLOGY

Depression is a common illness, with multifactorial etiology

- Genetic
- Epigenetic
- Adverse childhood experiences
- Adult trauma
- Social stress
- Substance use
- Diet and exercise
- Chronic illness, pain, inflammation
- Biological vulnerabilities

PARTICIPANT POLL QUESTION

Which medical conditions that increase risk of depression are more common in women?

GENDER DIFFERENCES - ETIOLOGY

Women have higher rates of

– autoimmune disease
- fibromyalgia
- thyroid dysfunction
- hyperandrogenism

Inflammation is a pathway from stress, medical disorders and unhealthy behaviors to depression

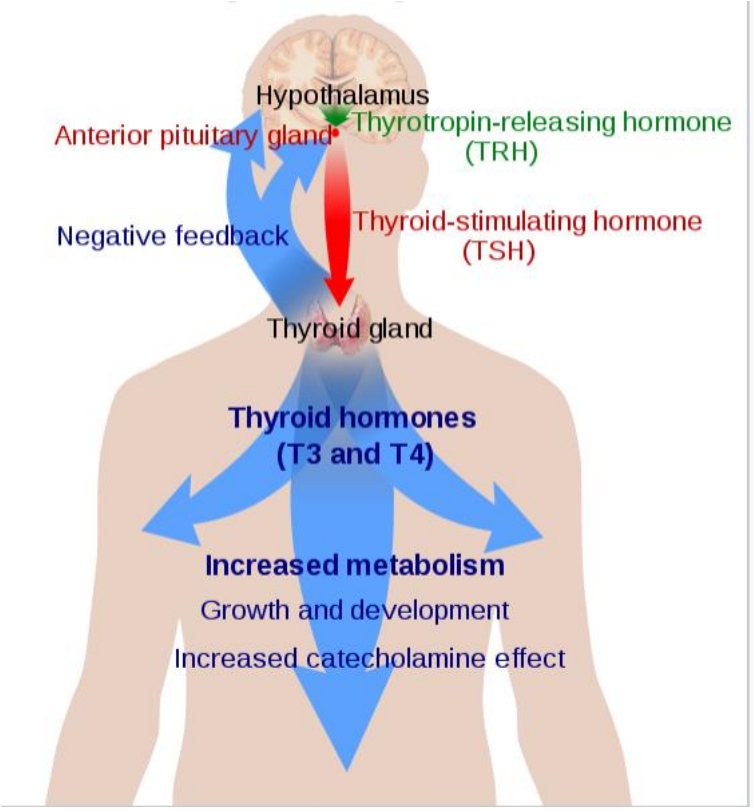
Inflammation promoted by

- Dietary factors
- Infections, injury
- Sleep deprivation
- Obesity
- Trauma, stress

Anti-inflammatory treatments are under investigation for depression treatment

DEPRESSION AND THYROID DISORDERS

- Hypothyroidism increases risk of major depression
- Thyroid disorders more common in women
- Most common is Hashimoto's thyroiditis, with anti-thyroid antibodies
- Prevalence of antithyroid antibodies is 10-18% in women, often asymptomatic
- Severity of hypothyroidism and required hormone dose shift over time
- Pregnancy suppresses antithyroid antibodies, and antibody levels rapidly increase postpartum
- 30-50% risk for hypothyroidism and hyperthyroidism postpartum in women with anti-thyroid antibodies



DEPRESSION AND SUBCLINICAL HYPOTHYROIDISM

- 3-8% of population (thyroid stimulating hormone [TSH] > 2.5)
- More common in women (8-14%)
- 80% of women with subclinical hypothyroidism have anti-thyroid antibodies
- Current recommendations to treat with thyroid hormone only if TSH >10mIU/L
- No cardiovascular or well-being benefit to treating lower TSH in general population

**** Treatment of subclinical hypothyroidism does relieve depression
**** Thyroid augmentation effective in STAR*D -24% response

Nierenberg et al 2006

HYPERANDROGENISM – MEDCIAL FEATURES

Oligomenorrhea/anovulation
Infertility
Hirsutism
Obesity
Acne
Alopecia
Insulin resistance
Type 2 diabetes
↑ dehydroepiandrosterone (DHEA-S)
↑ free testosterone
↑ 17-hydroxyprogesterone
↑ androstenedione
Low sex hormone binding globulin
Polycystic ovaries

10-12% prevalence

<u>Clinical Diagnoses</u>

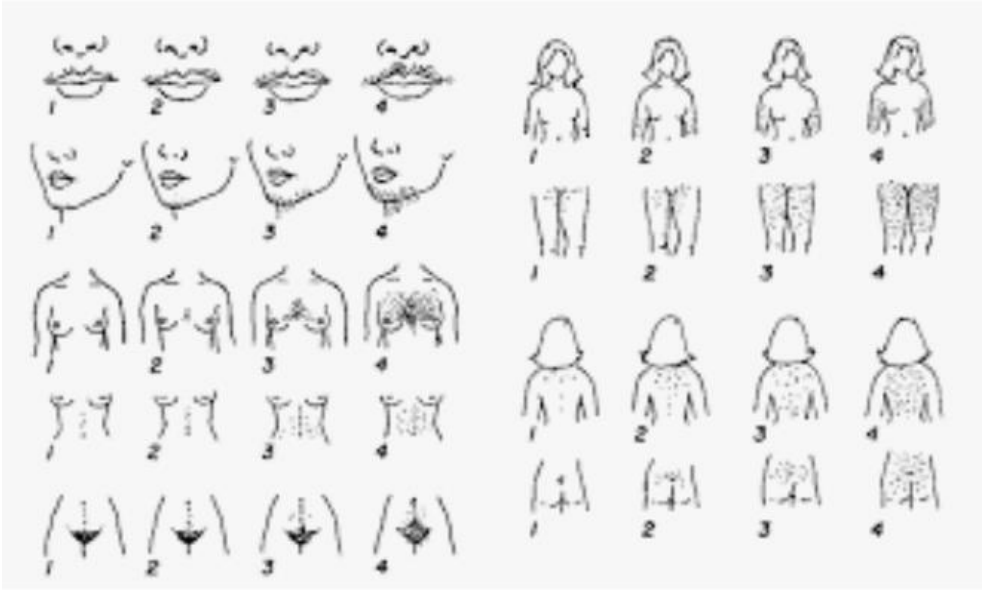
- *Polycystic ovarian syndrome (NIH diagnostic criteria)*
- *Idiopathic hirsutism*
- *Non – classical congenital adrenal hyperplasia*

HYPERANDROGENISM – MENTAL HEALTH

PCOS and hirsutism associated with

- Depression
- Bipolar disorder
- Suicide attempts
- Borderline personality disorder
- Bulimia; binge eating disorder
- PTSD
- Tic disorder; autism spectrum

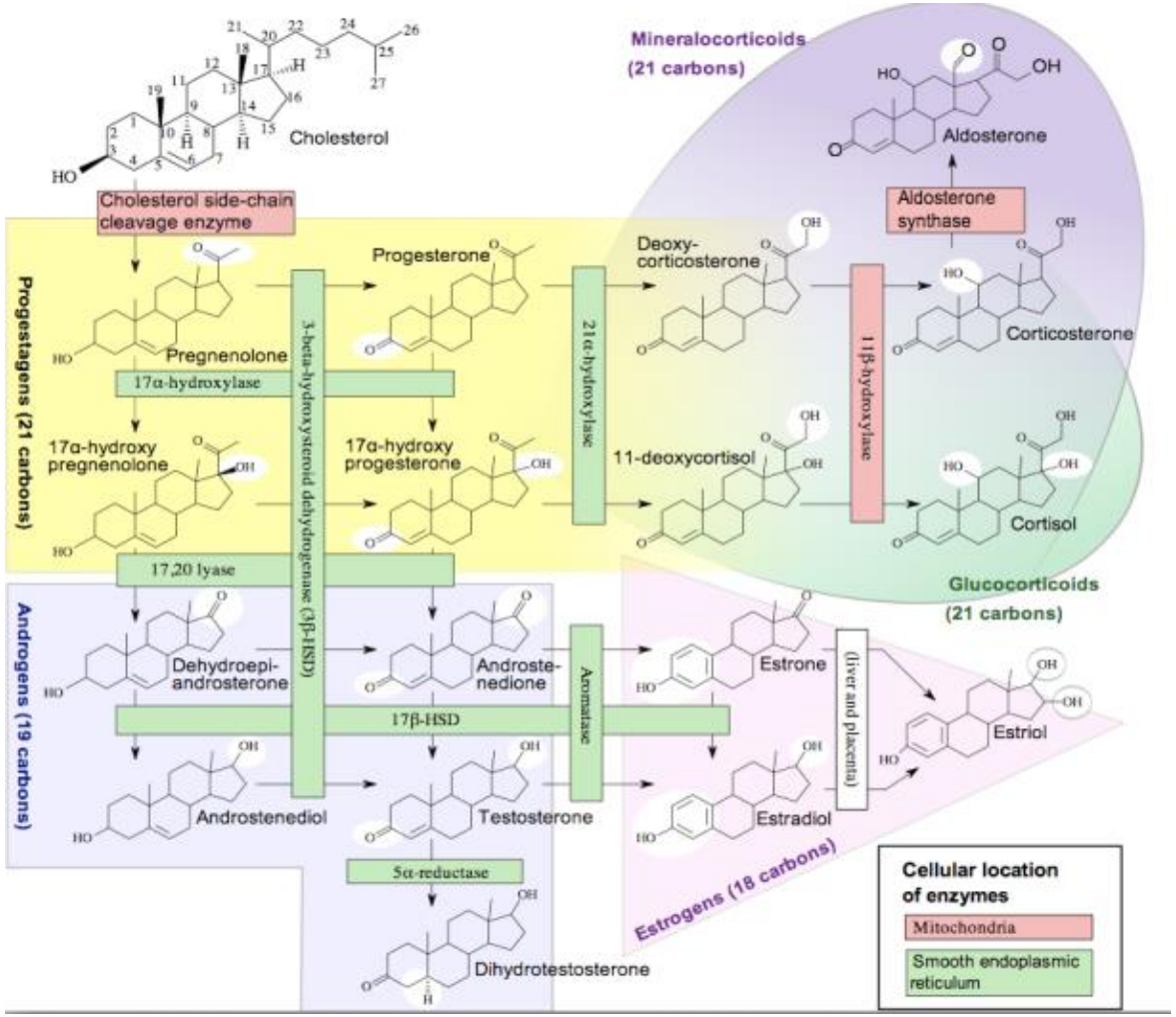
Tay et al., 2020; Cesta et al., 2016; Hung et al., 2014,
Hollinrake et al., 2007; Mansson et al., 2008
Cohen BE et al., 2012; Dobie D et al.2004



Ferriman-Gallwey Hirsutism Scale

REPRODUCTIVE STEROIDS AND DEPRESSION

- Some women are more sensitive to fluctuations in reproductive hormones
- Metabolism of steroid hormones differs among individuals



FERTILITY AND DEPRESSION

- Perceived stress not associated with lower estradiol or progesterone levels or anovulatory cycles Schliep et al., 2014

- Stress and depression do not affect in vitro fertilization (IVF) outcome Boivin et al., 2011

- Number of children not lower among women with lifetime depression Power et al., 2013

- Excessive exercise, dieting and bulimia do impair fertility

FERTILITY AND DEPRESSION

- 40-60% of women treated with clomiphene or gonadotropins report mood swings and irritability Choi et al., 2005

- Depression history associated with depression and anxiety during ovarian stimulation Zaig et al., 2013

- GnRH agonists (e.g. leuprolide) increase risk of depression, much more in women with a history of depression

Ben Dor et al., 2013, Warnock et al., 2000

HORMONAL CONTRACEPTION AND DEPRESSION

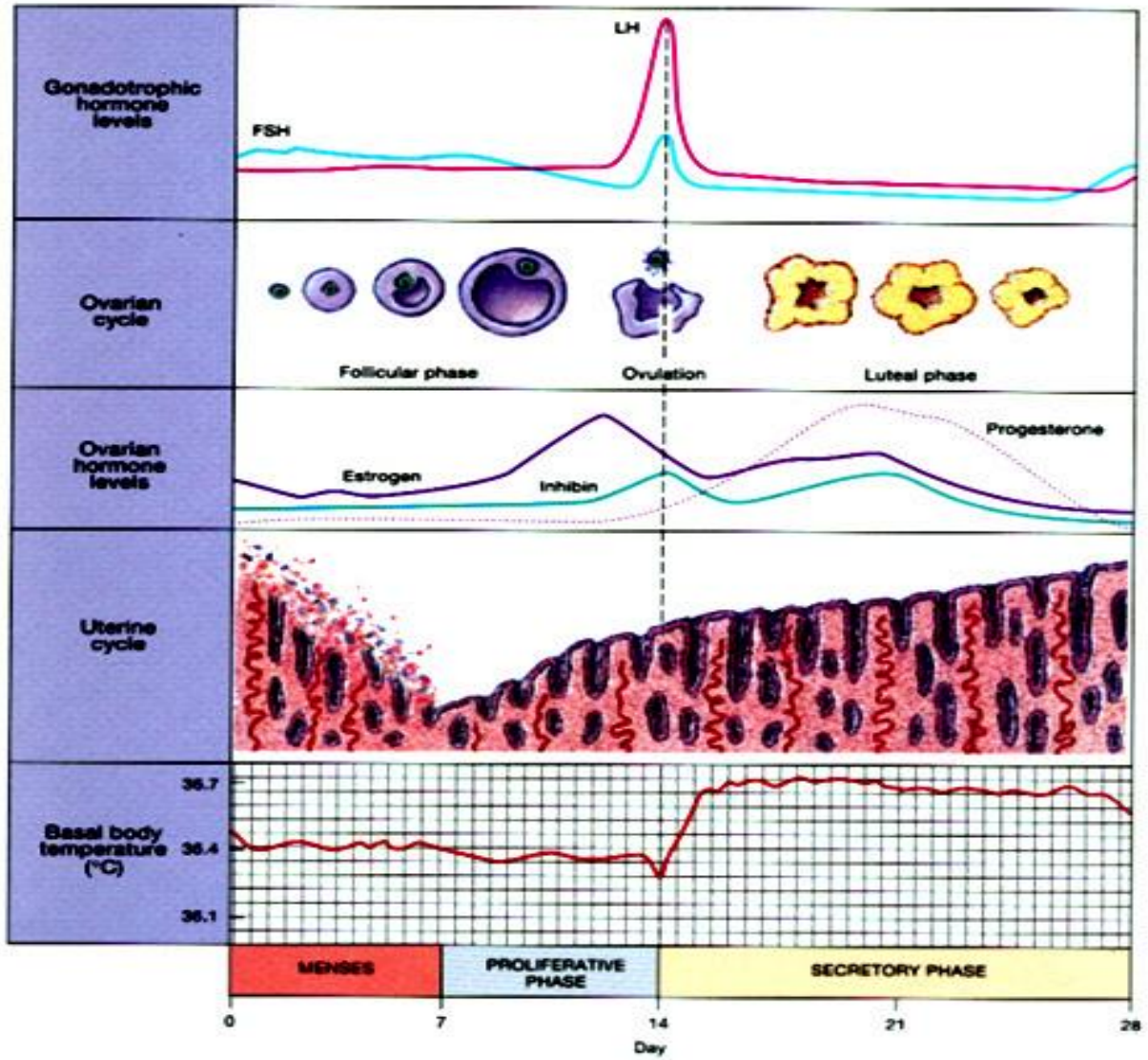
- 10%–21% of women using oral contraceptive experience adverse mood symptoms Segebladh et al., 2009, Sanders SA, 2001

- Some women meet criteria for PMDD while using oral contraceptives and respond to treatment with serotonin reuptake inhibiting antidepressants Yonkers et al 2017

- A history of mood disorders, premenstrual mood symptoms, somatic anxiety, eating disorders and risky alcohol use has been linked to increased mood lability and depressive symptoms during oral contraceptive use Kurshan & Epperson, 2006; Segebladh et al., 2009, Bengtsdotter et al., 2018, 2008, Joffe et al., 2003

- Women who discontinue oral contraceptive use due to mood side effects are at higher risk of suicide attempts and suicide Skovlund et al., 2016

MENSTRUAL CYCLE



PREMENSTRUAL DYSPHORIC DISORDER (PMDD)

PMDD is distinct from Major Depression

- The most characteristic symptoms of PMDD are mood lability and irritability rather than depression
- PMDD symptoms respond only to serotonin reuptake inhibiting antidepressants
- Serotonin reuptake inhibitors can reduce PMDD symptoms within hours
- Depression symptoms often intensify premenstrually but it is possible to have comorbid PMDD and major depression or bipolar disorder

PERINATAL DEPRESSION

- <u>Postpartum Major Depression</u>

  1/3 have chronic depression
  1/3 onset during pregnancy
  1/3 onset postpartum

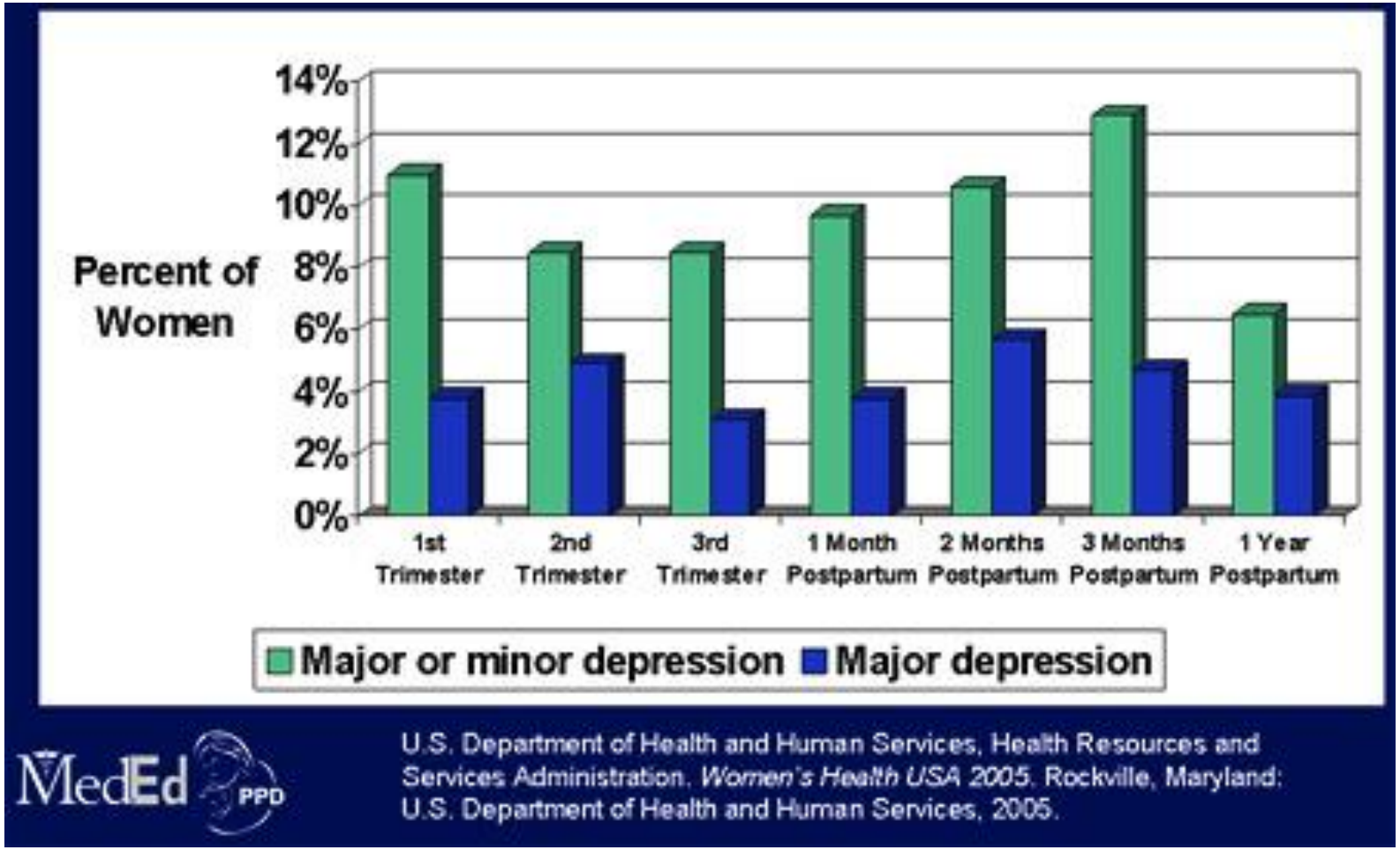
  Wisner et al., 2013

- Period prevalence Major Depression

  13% during pregnancy
  7 % postpartum

  Gaynes et al., 2005

PERINATAL DEPRESSION



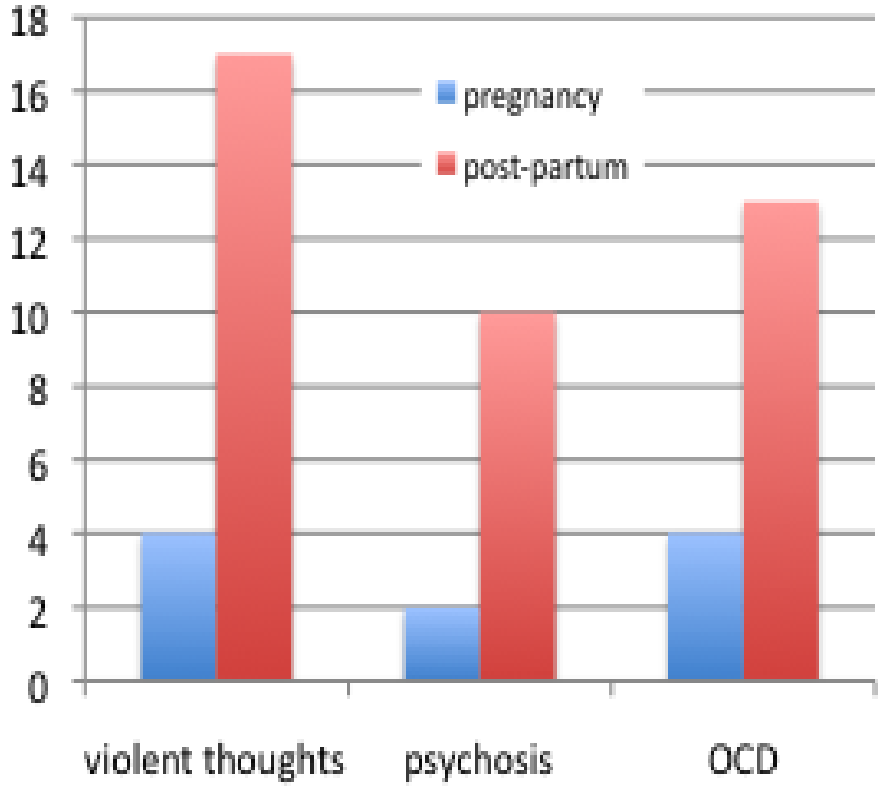
Risk factors less common in postpartum onset depression

Table 2. Psychiatric history and risk factors:
** p<.0001 * p<.01

Variable	Pregnancy Onset	Postpartum Onset
	N=113	N=116
Psychosocial and Medical risk factors		
Partner discord	19 (17%)	11 (10%) *
Social support low	21 (19%)	8 (7%) *
Abuse history	31 (27%)	18 (16%) *
Unplanned preg	33 (38%) N=86	20 (23%) N=86*
Psychiatric history		
Prior MDD	89 (79%)	52 (45%) **
Prior Non-puerperal depression	75 (70%)	47 (42%) **
Prior postpartum depression	28 (56%) N=50	6 (15%)N=41 **

Altemus et al., J Clin Psych 2013

Symptom profile differs in postpartum onset depression



Altemus et al., J Clin Psych 2013

Postpartum Psychosis

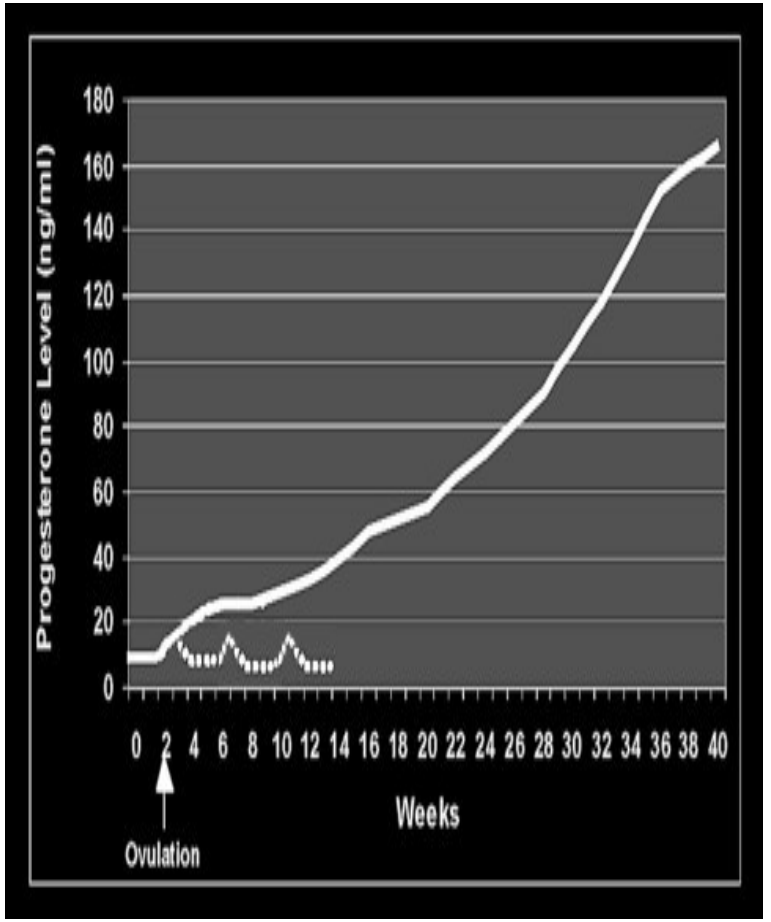
- 1% of new mothers
- 85% associated with bipolar I disorder
  - in some women may only occur postpartum
- Confusion, paranoia
- Excess energy, grandiose
- Medical emergency – usually requires hospitalization
- Risk of infanticide and suicide
  ***distinguish from ego dystonic, intrusive violent thoughts

PERINATAL DEPRESSION

Subclinical Mood Changes

Baby Blues – first 10 days postpartum
50-80% of new mothers
tearful, mood swings, insomnia

Hypomania – first 2 weeks postpartum
less common



Progesterone levels in pregnancy compared to menstrual cycle

Perinatal Depression Evaluation

- Need to distinguish typical pregnancy and infant care experience from depression
  - How long does it take to fall back asleep at night?
  - Can you sleep when the baby sleeps at night?
  - Can you have fun, enjoy baby and friends, when you are rested?
  - Are the worries bizarre or exaggerated?

Important to Identify Bipolar Depression

- 20% of postpartum major depression was bipolar I or bipolar II in large study using diagnostic interviews
  Wisner et al., 2013

- Early postpartum onset of major depression associated with later bipolar diagnosis
  Munk-Olsen T et al., 2012

Lactation

•Depression in pregnancy is associated with shorter duration of lactation

• Rapid weaning is associated with increased risk for depression postpartum Yusuff et al., 2015, Ystrom et al., 2012

• Sleep disruption and lactation difficulties can exacerbate depression

• Some women have transient dysphoria with milk let-down

PARTICIPANT POLL QUESTION

What are some benefits of treating depression during pregnancy and postpartum?

TREATMENT CONSIDERATIONS – PERINATAL DEPRESSION

Maternal depression linked to

•Reduced gestation length, prematurity only in women with comorbid major depression and PTSD Yonkers et al., 2014
and in women with higher cortisol levels in pregnancy Spicer et al., 2013
• Impaired fetal neurodevelopment
– activity/heart coupling and heart rate variability O'Connor TG et al., 2014

Maternal distress linked to

1) increased methylation of the HSD11B2 and FKBP5 genes in the placenta Monk et al., 2016

2) Offspring cortisol regulation, cognition and mental health
O'Donnell et al., 2014; Wadhwa, 2005, Kingston et al., 2015, Malaspina et al., 2008

TREATMENT CONSIDERATIONS – PERINATAL DEPRESSION

Infant benefits

- Language and social development
- Attachment
- Lactation success
- Growth
- Less depression, anxiety and disruptive behavior in childhood

Maternal benefits

- Maternal experience
- Family functioning

TREATMENT CONSIDERATIONS – PERINATAL DEPRESSION

Perinatal women are often more motivated to

1) consider psychotherapy

2) undergo trials to determine lowest effective medication doses

3) undergo trials of alternative medications

4) Increase healthy behaviors

TREATMENT CONSIDERATIONS – PERINATAL DEPRESSION

•Many pregnancies are unplanned

•Encourage contraception and pre-conception planning

•Increase non-pharmacologic interventions during pregnancy and lactation

- psychotherapy
- support groups
- light therapy
- social rhythm therapy
- apps and web-based resources

•Close follow-up, adaptive approach

TREATMENT CONSIDERATIONS – PERINATAL DEPRESSION

Non-medical interventions

- Physical activity
- Healthy eating
- Social support
- Spiritual resources
- Reduce substance use

TREATMENT CONSIDERATIONS – PERINATAL DEPRESSION

Pharmacologic interventions

- Risks of medication need to be weighed against risk of untreated illness
- Avoiding medication may not be the safest choice
- Few medications are known to be harmful to offspring

TREATMENT CONSIDERATIONS – PERINATAL DEPRESSION

Pharmacologic interventions

- Prefer treatments with known efficacy for that patient
- Prefer treatments which have more safety data
- Antidepressants have been well studied and risks are rare or mild

TREATMENT CONSIDERATIONS – PERINATAL DEPRESSION

- Focus on sleep as marker of severity and as impeding recovery
  - *reduced total sleep time is associated with premature birth and gestational diabetes*

- Support consideration of partial or no lactation
  - *well controlled studies do not demonstrate health benefits of lactation vs. bottle-feeding*

DEPRESSION AND MENOPAUSE TRANSITION

- Increased risk of recurrent depression relapse (4-8 fold) in perimenopause Freeman et al., 2014

- Increased risk (2-fold) of first-onset depression in perimenopause Cohen et al., 2006, Freeman et al., 2006

- Surgical or chemical menopause produces more severe depression, vasomotor symptoms, and pain Aziz et al., 2005

- Surgical menopause without hormone replacement increases lifetime risk for anxiety, depression and dementia Faubion et al., 2015

Risk Factors for Perimenopausal Depression

- Role transitions
- Sleep disruption
- Pain
- Vasomotor symptoms
- Hormonal fluctuations
  - higher risk with surgical or abrupt medical menopause

TREATMENT CONSIDERATIONS - PERIMENOPAUSE

- May need to augment maintenance treatment
- Address sleep disruption
- Short term estradiol treatment effective for perimenopausal depression, independent of vasomotor symptoms Schmidt et al., 2000; Soares et al., 2001; Joffe et al., 2011
- Estrogen augmentation of antidepressant medication also may be effective during perimenopause Morgan et al., 2005
- Some women have adverse mood reactions to progesterone or progestin in hormone replacement therapy

SUMMARY

•Women have higher rates of unipolar depression and most anxiety disorders

•Much individual variability in response to reproductive events and hormone challenges

•History of depression elevates risk of recurrence during pregnancy, postpartum, infertility treatment, oral contraceptive use and menopause

•Growing evidence of adverse effects of depression during pregnancy and postpartum on offspring

SUMMARY

Better understanding of medical vulnerabilities, psychosocial stressors and reproductive risk factors can help women anticipate, prevent, and manage depression.

PRESENTER CONTACT INFORMATION

Thanks!!

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