Depression and Women Across the Reproductive Lifecycle

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Learning Objective 1

Identify factors that increase the risk of mood disturbance in women at key time points when hormonally-related triggers are present (e.g., menses, pregnancy, postpartum, perimenopause)
Learning Objective 2

Design and implement treatment plans to manage the mood symptoms in women at various life stages
Audience Response

Has the Women’s Health Initiative impacted the way you treat your peri-menopausal and menopausal patients

A. Yes, I discourage patients from taking estrogen
B. It has made no difference
C. Data is mixed, so I am cautious
D. I ignore it and recommend estrogen when appropriate
Gonadal Steroids, Like All Steroid Hormones, are Derivatives of Cholesterol

Principles

- Reproductive hormones wire and rewire the brain
- Reproductive hormones regulate brain circuitry
- Changes in reproductive hormones alter brain states of clinical relevance
- Reproductive endocrine-related mood disorders account for a substantial amount of morbidity and mortality
- These disorders are NOT hormone deficiencies
- Reproductive steroids are both context-dependent and context-determining

Reproductive Hormones
Wire and Rewire the Brain
Reproductive Hormones Regulate Brain Circuitry
Steroids Regulate PFC Functional Correlations With Left Hippocampal Formation Activity

PFC = prefrontal cortex
K Berman et al. Unpublished data.
OFC Activity in Response to Emotional Stimuli in the Context of Behavioural Inhibition Across the Menstrual Cycle

OFC = orbitofrontal cortex
Periods of Reproductive Endocrine Change are Associated With Altered Mood States and Reproductive Endocrine-Related Mood Disorders Account for Substantial Morbidity and Mortality

- Puberty
- Menstrual Cycle
- Puerperium
- Perimenopause
DHEA = dehydroepiandrosterone

Gene Network

Gene network regulating puberty

Reproductive Endocrine-related Mood Disorders

- Premenstrual dysphoria
- Perinatal depression
- Perimenopausal depression
Reproductive Endocrine-related Mood Disorders

- Premenstrual dysphoria
  - Prevalence – 5%
  - Cause of 14.5 million Disability Associated Live Events annually in US
  - Requires prospective confirmation of restriction of symptoms to the luteal phase

Efficacy of GnRH-A in the Symptoms of PMDD

GnRH-A = gonadotropin-releasing hormone agonist; PMDD premenstrual dysphoric disorder.
Central Nervous System Effects of GnRH Agonist & Gonadal Steroid Replacement

GnRH-A = gonadotropin-releasing hormone agonist; IM = intramuscular; QM = every month; BID = twice a day.
Steroid Precipitation of PMDD Symptoms

PMDD = premenstrual dysphoric disorder
Differential Brain Regional Activation by Ovarian Steroids in PMDD

**Subgenual Cingulate**

(-6, 20, -10)

\[ p = .0002 \]

PMDD = premenstrual dysphoric disorder

Schmidt PJ, unpublished data.
Differential Brain Regional Activation by Ovarian Steroids in PMDD

PMDD = premenstrual dysphoric disorder
Schmidt PJ, unpublished data.
PMDD: Is it Triggered by the Level of Steroid or the Change in Level of Steroid?
Reproductive Endocrine-related Mood Disorders

- Premenstrual Dysphoria
- Perinatal Depression
- Perimenopausal Depression
Perinatal Depression

- Prevalence – 10% - 15% (MDE = 7.5%; mDE = 6.5%)
- Suicide is the leading cause of maternal death

MDE = major depressive episode; mDE = minor depressive episode
Background: Perinatal Depression

- **COMMON**
  - 10%-15% prevalence
  - 4 million women give birth annually in U.S.; one-half million with perinatal depressive disorder
  - Most common, unrecognized complication of perinatal period
    - Compare to the prevalence rate of gestational diabetes at 2%-5%

- **MORBID**
  - Devastating consequences for patient and family
    - Low maternal weight gain, preterm birth
    - Impaired bonding between mother and infant
    - Increased risk of suicide and infanticide

- **MISSED**
  - No practice guidelines or routine screening
  - Symptoms often different from “classic DSM-IV depression”

Distinguishing Characteristics of Perinatal Mood Symptoms

- Anxiety or agitation
- Depressed mood
- Sadness, weepiness
- Irritability
- Hypervigilance about the baby
- OR lack of interest in the newborn
- Impaired concentration or feeling overwhelmed
- Feelings of dependency or guilt

Other Facts and Dilemmas

- There is no free lunch
- Inadequacy of database
- During pregnancy, there are medications to avoid, but….
- Pregnancy affects medication levels
  - Increased volume of distribution, hepatic blood flow
  - Decreased plasma binding proteins
  - Effects of reproductive steroid on metabolic enzymes

Profound Neuroendocrine Changes at Time of Birth

What Is the Hormone Trigger in Perinatal Depression?

PLACEBO  E2+ PROG  PLACEBO

Leuprolide acetate

BASELINE  HYPOGONADAL  ADDBACK  WITHDRAWAL

0  4  8  12  16  20  24

E2 = estradiol; PROG = progesterone
Weekly Cornell Depression Scale Scores (One Subject)

PPD Study: Cornell Depression Score

(Mean ±SEM)
PPD = Postpartum depression
These Disorders
Are NOT Hormone Deficiencies
Reproductive Endocrine-related Mood Disorders

- Premenstrual Dysphoria
- Perinatal Depression
- Perimenopausal Depression
Perimenopausal Depression

- Prevalence – 20%
- Is associated with a 50% increase in cardiovascular mortality

E2 Withdrawal Precipitates Depressive Symptoms in Asymptomatic Women With a Past Perimenopausal Depression

E2 = estradiol; PMD = perimenopausal depression; CESD = Center for Epidemiologic Studies Depression Scale; DB = double. Schmidt PJ, et al. unpublished data
Therapeutic Trial of Estradiol, SERM, and Phytoestrogen in Perimenopausal Depression (n = 38)

SERM = selective estrogen-receptor modulator; HDRS = Hamilton Rating Scale for Depression; Tx*Time = treatment by time. Schmidt PJ. Unpublished data.
Baseline Characteristics of Participants in Randomized, Controlled Trials

<table>
<thead>
<tr>
<th>Characteristic (Hormone Therapy; Placebo)</th>
<th>WHI E+P</th>
<th>WHI E</th>
<th>WHIMS E+P</th>
<th>WHIMS E</th>
<th>WHISCA E+P</th>
<th>WHISCA E</th>
<th>HERS E+P</th>
<th>ESPRIT E</th>
<th>EMS E+P</th>
<th>WISDOM E+P</th>
<th>ULTRA E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>8506;8102</td>
<td>5310;5429</td>
<td>2229;2303</td>
<td>1464;1483</td>
<td>690;726</td>
<td>434;452</td>
<td>1380;1383</td>
<td>513;504</td>
<td>70;72</td>
<td>2196;2189</td>
<td>191;185</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>63.2;63.3</td>
<td>63.6;63.6</td>
<td>63.2;63.3</td>
<td>63.6;63.6</td>
<td>73.69;73.86</td>
<td>74.01;74.02</td>
<td>67;67</td>
<td>62.3;62.9</td>
<td>75;74.5</td>
<td>63.3;63.3</td>
<td>66.8;66.7</td>
</tr>
<tr>
<td>Nonwhite race, %</td>
<td>16.1;16.0</td>
<td>24.5;24.9</td>
<td>-</td>
<td>17.3;16.4</td>
<td>8.4;7.0</td>
<td>14.09;13.08</td>
<td>12;10</td>
<td>3;3</td>
<td>4.3;9.7</td>
<td>1;1.4</td>
<td>7.2;8.1</td>
</tr>
<tr>
<td>Previous or current HT, %</td>
<td>26.1;25.6</td>
<td>47.8;48.9</td>
<td>21.8;22.4</td>
<td>45.8;44.7</td>
<td>21.2;22.6</td>
<td>49.54;46.24</td>
<td>1.7;1.7</td>
<td>12;10</td>
<td>31.4;23.6</td>
<td>55;54.3</td>
<td>-</td>
</tr>
<tr>
<td>Hysterectomy age &lt;40 y, %</td>
<td>-</td>
<td>39.8;39.8</td>
<td>-</td>
<td>-</td>
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<td>-</td>
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</tr>
<tr>
<td>Hysterectomy age 40–49 y, %</td>
<td>-</td>
<td>43.2;42.2</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Bilateral oophorectom, %</td>
<td>-</td>
<td>39.5;42.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>Never pregnant, %</td>
<td>10.1;10.3</td>
<td>9.3;8.5</td>
<td>-</td>
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</tbody>
</table>

## Results of Hormone Therapy Trials

<table>
<thead>
<tr>
<th>Outcome</th>
<th>E+P vs. Placebo</th>
<th>E vs. Placebo</th>
<th>E vs. Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>Differences in events per 10,000 women-years (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive breast</td>
<td>1.25 (1.07–1.46)</td>
<td>8 (3–14) more</td>
<td>0.77 (0.62–0.95)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>0.75 (0.57–1.00)</td>
<td>Not significant</td>
<td>1.11 (0.82–1.50)</td>
</tr>
<tr>
<td>Lung</td>
<td>1.23 (0.92–1.63)</td>
<td>Not significant</td>
<td>1.17 (0.81–1.69)</td>
</tr>
<tr>
<td>Endometrial</td>
<td>0.78 (0.52–1.16)</td>
<td>Not significant</td>
<td>Not reported</td>
</tr>
<tr>
<td>Ovarian</td>
<td>1.58 (0.77–3.24)</td>
<td>Not significant</td>
<td>Not reported</td>
</tr>
<tr>
<td>Cervical</td>
<td>1.44 (0.47–4.42)</td>
<td>Not significant</td>
<td>Not reported</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(CHD death and total MI)</td>
<td>1.22 (0.99–1.51)</td>
<td>Not significant</td>
<td>0.95 (0.78–1.15)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.34 (1.05–1.71)</td>
<td>9 (2–15) more</td>
<td>1.36 (1.08–1.71)</td>
</tr>
<tr>
<td>Thromboembolic events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>1.88 (1.38–2.55)</td>
<td>12 (6–17) more</td>
<td>1.47 (1.06–2.05)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1.98 (1.36–2.87)</td>
<td>9 (4–14) more</td>
<td>1.37 (0.90–2.07)</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-reported new diagnosis</td>
<td>0.79 (0.67–0.93)</td>
<td>15 (4–26) less</td>
<td>0.88 (0.77–1.01)</td>
</tr>
<tr>
<td>requiring treatment with drugs</td>
<td></td>
<td></td>
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</tr>
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<tr>
<td></td>
<td>HR (95% CI)</td>
<td>Differences in events per 10,000 women-years (95% CI)</td>
</tr>
<tr>
<td>Fractures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip</td>
<td>0.67 (0.47–0.95)</td>
<td>6 (1–10) less</td>
</tr>
<tr>
<td>Vertebral</td>
<td>0.68 (0.48–0.96)</td>
<td>6 (1–11) less</td>
</tr>
<tr>
<td>Total fractures</td>
<td>0.76 (0.69–0.83)</td>
<td>46 (29–63) less</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1.04 (0.91–1.18)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Breast cancer mortality</td>
<td>1.96 (1.00–4.04)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Lung cancer mortality</td>
<td>1.71 (1.16–2.52)</td>
<td>5 (1–8) more</td>
</tr>
<tr>
<td>Gallbladder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gallbladder disease (cholecystitis and cholelithiasis)</td>
<td>1.61 (1.30–2.00)</td>
<td>20 (11–29) more</td>
</tr>
<tr>
<td>Cognitive function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probable dementia</td>
<td>2.05 (1.21–3.48)</td>
<td>22 (5–39) more</td>
</tr>
<tr>
<td>Mild cognitive impairment</td>
<td>1.07 (0.74–1.55)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall urinary incontinence (stress, urge, or mixed)</td>
<td>1.39 (1.27–1.52)</td>
<td>872 (591–1153) more</td>
</tr>
</tbody>
</table>

Reproductive Steroids Are Both Context-Dependent and Context-Determining

- Susceptibility

- What do we mean by gene : environment interactions?

Estradiol Effects in the Forced Swim Test: Strain Differences

Wistar Hannover rat and Long Evans rat.
Strain-dependent Effects of Estradiol in the Forced Swim Test

Biology and Environment Meet at the Level of the Dance Partners

- SMRT, high-fat diet, and obesity/insulin resistance

SMRT = silencing mediator of retinoid and thyroid hormone receptors
High-Fat Diet Induced Severe Obesity in SMRTmRID1 Mice

SMRT = silencing mediator of retinoid and thyroid hormone receptors; WT = wild type
NC = normal control; HFD = high-fat diet.
Effects of Genetic Differences are Unmasked by Environment

- SMRT mutation, high-fat diet, and obesity/insulin resistance
- GABA-A receptor mutation, pregnancy, and depression

SMRT = silencing mediator of retinoid and thyroid hormone receptors
Deficient NS Signaling: Postpartum “Depression” and “Infanticide”

NS = neurosteroid; WT = wild type Wistar; THIP = 4,5,6,7-tetrahydroisoaxazolo-[5,4-c]pyridin-3-ol
Embrace the Uncertainty!
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMS</td>
<td>Estrogen Memory Study</td>
</tr>
<tr>
<td>ESPRIT</td>
<td>Oestrogen in the Prevention of Reinfarction Trial</td>
</tr>
<tr>
<td>HERS</td>
<td>Heart and Estrogen/Progestin Replacement Study</td>
</tr>
<tr>
<td>HT</td>
<td>hormone therapy</td>
</tr>
<tr>
<td>MI</td>
<td>myocardial infarction</td>
</tr>
<tr>
<td>P</td>
<td>progestin</td>
</tr>
<tr>
<td>PE</td>
<td>pulmonary embolism</td>
</tr>
<tr>
<td>SBP</td>
<td>systolic blood pressure</td>
</tr>
<tr>
<td>ULTRA</td>
<td>Ultra-Low-Dose Transdermal Estrogen Assessment</td>
</tr>
<tr>
<td>WHI</td>
<td>Women’s Health Initiative</td>
</tr>
<tr>
<td>WHIMs</td>
<td>Women’s Health Initiative Memory Study</td>
</tr>
<tr>
<td>WHISCA</td>
<td>Women’s Health Initiative Study of Cognitive Aging</td>
</tr>
<tr>
<td>WISDOM</td>
<td>Women’s Intl Study of Long Duration Oestrogen After Menopause</td>
</tr>
<tr>
<td>CHD</td>
<td>coronary heart disease</td>
</tr>
<tr>
<td>HR</td>
<td>hazards ratio</td>
</tr>
<tr>
<td>CI</td>
<td>confidence intervals</td>
</tr>
<tr>
<td>E + P</td>
<td>estrogen plus progestin</td>
</tr>
<tr>
<td>E</td>
<td>estrogen only</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
</tbody>
</table>
Questions & Answers