

Treatment of Psychiatric Disorders Across the Female Life Cycle

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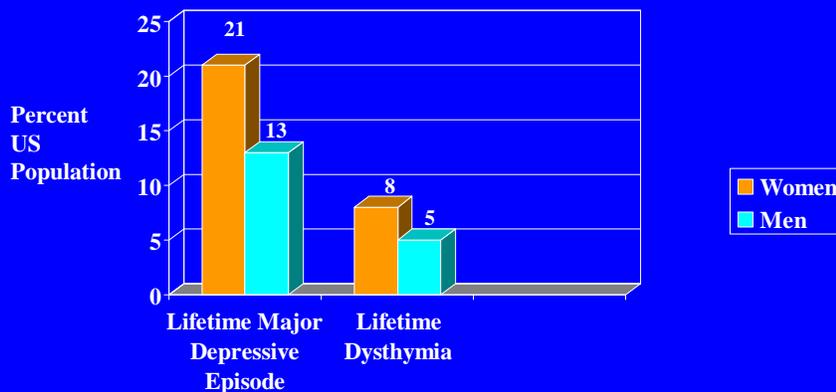
Objectives

- **Overview of the function and possible psychological effects of estrogen, testosterone, and progesterone throughout the female life cycle**
- **Review the effects of estrogen, testosterone, and progesterone on the female brain, with a focus on serotonin receptor functioning**
- **Review the appropriate hormonal lab tests for evaluating a woman with depression, anxiety, decreased libido, cognitive dysfunction, and low energy**

Objectives (continued)

- Describe the recent advances and the understanding and treatment of psychiatric disorders throughout the female life cycle, including pre-menstrual dysphoric disorder, pregnancy, the postpartum, breast feeding, the peri-menopause and menopause

Estimated Prevalence of Depressive Disorders in Women and Men



Kessler, et al. Arch Gen Psychiatry. 1994; 51; 8-19.

**Hormones and the Mind:
A Woman's Guide To Enhancing
Mood, Memory, and Sexual Vitality**

Edward L. Klaiber, M.D.

Copyright 2001
HarperCollins Publishers

Hormones and the Mind

Hormones of significance to a woman's mental health

- **Estradiol**
- **Progesterone**
- **Testosterone**
- **Thyroid Hormones**
- **FSH**
- **LH**
- **Prolactin**

Consequences of Hormonal Imbalances in Woman

- **Mood Disorders**
- **Anxiety**
- **Cognitive dysfunction**
- **Indecisiveness**
- **Decreased libido**
- **Sexual dysfunction**
- **Many medical risks**

Effects of Estrogen on the Brain

- **Increases the amounts of mood regulating neurotransmitters: serotonin, norepinephrine, dopamine and acetylcholine**
- **Increases the density of neurotransmitter receptors on the surface of nerve cells**
- **Maintains the integrity of dendrites**
- **Works in concert with neuronal growth factors**
- **Increases neuronal “connectivity”, helping to regulate emotional states and cognition**
- **Is required for maximal blood flow to locations in the brain which regulate emotion and cognitive functioning**

Estrogen and Serotonin

- **Estrogen inhibits the breakdown of serotonin by MAO, hence increasing brain serotonin**
- **Estrogen enhances brain serotonin synthesis**
- **Estrogen increases the number and sensitivity of serotonin receptors**

Estrogen and Cognition

- **Increases choline acetyltransferase which synthesizes acetylcholine**
- **Facilitates the uptake of choline into brain cells, which is required to synthesize acetylcholine**
- **Facilitates neuronal networking**
- **Promotes nerve growth factors – neural protective**
- **Inhibits MAO, hence prolongs the availability of serotonin, norepinephrine and acetylcholine**
- **Has antioxidant properties that protects nerve cells from free radical damage**

Estrogen and Testosterone

- **Estrogen is necessary to stimulate receptors for testosterone**
- **Testosterone acts on the brain to regulate libido and sexual functioning as well as cognitive function – learning and memory, and energy**
- **Meta-analysis of 26 studies has demonstrated that appropriate estrogen supplementation can effectively treat depression in women, and that the addition of testosterone further enhances responsiveness**

Role of Testosterone in Women

- **Necessary for libido and sexual functioning**
- **Antidepressant effect on the female brain**
- **Improves energy, vitality and well-being**
- **Improves cognition, decision making, learning**
- **Stimulates bone growth & muscle development**
- **Requires estrogen to stimulate testosterone receptors**

The Progesterone Factor

- **Inhibits estrogen receptors**
- **Appears to dampen the effect on brain receptors for serotonin and norepinephrine**
- **Increases brain MAO activity**
- **Decreases libido and sexual functioning by competing with testosterone**
- **Stimulates brain GABA receptors**
 - **Reduces anxiety**
 - **Induces sleepiness**

Need for Progesterone

- **Necessary to protect the uterus against endometrial hyperplasia from estrogen, which can increase the risk of uterine cancer**
- **Use of vaginal suppositories of progesterone can limit the negative effects of progesterone on mood and cognition**

Estrogen Replacement Therapy

What are the risks??

- **Breast Cancer, after long term use**
- **Thrombophlebitis**
- **Pulmonary embolism**
- **Mastalgia (breast tenderness)**
- **Increased Gallbladder Disease**

Estrogen Replacement Therapy

What are the benefits?? Decreased Incidence:

- **Hot flashes**
- **Night sweats**
- **Insomnia**
- **Cardiac disease (???)**
- **Osteoporosis**
- **Stroke (???)**
- **Macular Degeneration**
- **Fibromyalgia**
- **Colon Cancer**
- **Overall cancer deaths**
- **Deaths from all causes**
- **Mood disorders**
- **Rx-resistant depression**
- **Cognitive dysfunction**
- **Indecisiveness**
- **Alzheimer's disease (???)**
- **Libido dysfunction**
- **Sexual dysfunction**

Hormone Replacement Therapy: Remains Controversial

Women's Health Initiative

Journal of the American Medical Association; July 17, 2002

- **Prempro versus Premarin versus Placebo**
- **Highly criticized study – rebuttals in process**
- **Mean age = 63 years old**
- **Women were locked into limited types of HRT**
- **Did not control for pre-existing vascular disease**
- **Does not address safety of HRT in peri-menopausal women (ages 45-60)**

About Testosterone and Women

- **Women's bodies make 0.3mg testosterone/day**
- **Men's bodies make 7 mg testosterone/day**
- **Secreted by the ovaries and adrenal glands**
- **98% is bound to proteins in the blood**
- **Sex Hormone Binding Globulin (SHBG)**
- **2% circulates freely in the blood**
- **Free testosterone is the physiologically active form**

Testosterone Replacement Therapy In Women

Brand	Generic	Route**	Dose in mg
Estratest	EE/MT*	Oral	1.25/2.5
Estratest HS	EE/MT*	Oral	0.625/1.25
None	Compounded MT	Oral	0.3-1.2

* EE = esterified estrogen; MT = methyltestosterone

** Testosterone also available in other formulations: injectible;
transdermal patch; depot; dermal gel; subcutaneous pellets

Laboratory Workup

Hormonal Lab Assessment

- **Estradiol**
- **Progesterone**
- **Testosterone**
- **Free Testosterone**
- **Prolactin**
- **FSH**
- **Thyroid Function Tests:**
 - **T3, T4, Free T4, TSH**

Premenstrual Dysphoric Disorder

Decades of Menstrual Cycles

- Between the ages of 20 and 50, woman experience a 40 to 50% decline in Estrogen and Testosterone levels
- During the post-luteal phase, there is a five fold decrease in estrogen levels over 2-3 days
- PMS and PMDD occur during the post-luteal phase

Diagnostic Criteria for PMDD

Five of the following symptoms (with at least one *) must occur during the week before menses and remit within days of menses

- Irritability*
- Affective lability*
- Decreased interest
- Poor concentration
- Low energy
- Change in appetite
- Depressed mood or hopelessness*
- Tension or Anxiety*
- Change in sleep
- Feeling overwhelmed
- Feeling out of control
- Physical Symptoms (breast tenderness\bloating)

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC 1994

PMDD Distinct from Depression

- Symptoms resolve within days of menses onset
- Tied to the menstrual cycle
- Does not occur in men
- Pregnancy resolves symptoms in PMDD
- Usual relapse of symptoms within one to two cycles after medication discontinuation
- Associated unique physical symptoms
 - breast tenderness and bloating

Endicott, J, et al. J Women's Health and Gend Based Med. 1999; 8:663-679.

Prevalence of Major Depression in Women With PMDD

Lifetime Prevalence of Major Depression

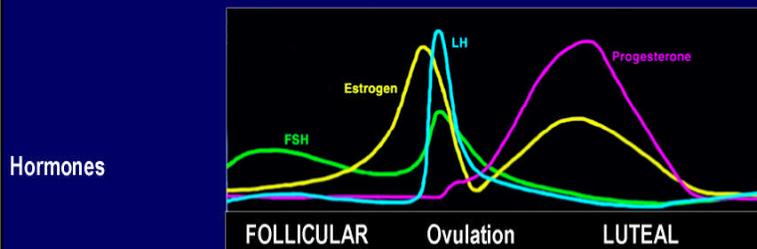
- Women with PMDD: 45% to 70%
- General Female Population: 21.3%

PMDD: Role of Serotonin versus Norepinephrine

- After 3 screening months, 189 women were randomized to sertraline, desipramine or placebo for 3 months of double blind Rx
- Responder defined as having a >50% reduction in the Penn Daily Symptom Report (DSR)
- Responders
 - Sertraline = 65%
 - Desipramine = 36%
 - Placebo = 29%

Freeman, et al. Arch Gen Psychiatry. 1999; 56: 932-939

Proposed Etiology of PMDD^{1,2}



- ♦ Symptoms are temporally associated with fluctuations in reproductive hormones
- ♦ Serum levels of reproductive hormones *do not predict* who will have PMDD

1. Britton K, et al. *Nature*. 1998;392:869-870.
2. Mortola J. *Trends Endocrinol Metab*. 1996;7:184-189.

Intermittent Luteal Phase Treatment with SSRIs for PMDD

Sertraline and Fluoxetine both equally clinically effective

- **Sertraline (Zoloft)**
 - T1/2 = 30 hours
 - None in serum for at least 10 days/cycle
 - Only dopamine sparing SSRI
 - Rapid 5 day washout if become pregnant
- **Fluoxetine (Prozac, Sarafem)**
 - T1/2 = 14 days
 - Level never drops below 50% with pulse treatment 14d/cycle
 - No dopamine sparing: may increase Prolactin level
 - Minimum 70 day washout if become pregnant

Halbreich et al. J Clin Psychiatry. 1997; 58: 399-402

Young, et al. J Clin Psychiatry. 1998; 59: 76-80

Pregnancy

Expert Consensus Guidelines - 2001

Altshuler, L. et al.; Postgrad Med Special Report.
2001 (March): 1-116

Since the publication of these guidelines,
newer literature has changed our understanding
of the risks of SSRIs during pregnancy,
especially during the third trimester.

“the degree of severity of maternal disease appears
to represent the most relevant parameter to take
this clinical decision”

Gentile S.; The safety of newer antidepressants in pregnancy
and breastfeeding.; Drug Saf. 2005;28(2):137-52.

Antidepressant Use During Pregnancy

- TCAs
 - Although all are Schedule D, studies since 1995 show minimal risks
- SSRIs
 - All are Schedule C, except paroxetine = Schedule D
 - Risk/Benefit discussion should dictate treatment
 - Estimated that at least 80,000 American women take SSRIs during pregnancy each year
- Newer Atypical Antidepressants (bupropion, mirtazapine, nefazodone)
 - Should not be used as first line
 - Too little information available at this time

SSRIs and Neonatal Withdrawal

- “assessed cases of neonatal convulsions and neonatal withdrawal syndrome associated with (SSRIs)” . . . reported to the World Health Organization (WHO) up to November 2003 . . . a total of 93 suspected cases:
 - Paroxetine = 64
 - Fluoxetine = 14
 - Sertraline = 9
 - Citalopram = 7

Sanz EJ, et al.; Lancet. 2005 Feb 5;365(9458):482-7.

Neonatal Withdrawal Symptoms seen with third trimester SSRI use

- Jitteriness
- Respiratory difficulty
- Pre-term delivery
- Low birth weight infants
- Lower APGAR scores
- Rare seizures
- Prolonged hospitalization for the newborn
- Need for specialized nurseries

SSRIs and Placental Passage

- Placental transfer of antidepressants and their metabolites were evaluated
- 38 pregnant women taking citalopram, fluoxetine, paroxetine, or sertraline participated
- Maternal & umbilical cord blood samples were obtained
- 86.8% of umbilical cord samples showed antidepressant
- The mean ratios of umbilical cord to maternal serum concentrations ranged from 0.29 to 0.89
- Lowest ratios were for sertraline and paroxetine
- Highest ratios were for citalopram and fluoxetine
- Maternal doses of sertraline and fluoxetine correlated with umbilical cord concentrations

Hendrick, V, et al.; Am J Psychiatry 160:993-996, May 2003

Prenatal Antidepressant Treatment and Childhood Neurodevelopment

- Nulman et al studied children of mothers who used antidepressants during pregnancy
 - TCAs (n=80)
 - SSRI fluoxetine (n=55)
- Neurodevelopment assessed from 16 to 86 months (7 years)
- Compared with controls (n=84), no significant differences in global IQ, language development or behavioral development

Nulman et al. N Engl J Med. 1997; 336:258-262.

Mood Stabilizer Use During Pregnancy

- **Lithium**
 - First line choice
 - Epstein's Anomaly in 0.1% of pregnancies
- **Carbamazepine**
 - Second line choice
 - Neural Tube Defects in 1% of pregnancies
- **Divalproex**
 - Third line choice
 - Neural Tube Defects in 4% of pregnancies

The Postpartum

The Postpartum Period

- **Massive hormonal decline in estrogen and progesterone levels during the first 24 hours post delivery**
- **Estrogen levels drop from 1000's of picograms during pregnancy to \leq 100 picograms postpartum**
- **Numerous other physiological changes are also occurring**

Postpartum Depression

Time of Onset Inconsistently Defined

- **Literature definitions: between 4 weeks to 6 months following delivery**
- **DSM-IV definition: within 4 weeks of delivery**
- **DSM-IV criteria for Postpartum Depression same as those for Major Depression**

Treatment of Postpartum Depression

- **Reassurance and support**
 - Support groups
- **Individual, marital or group psychotherapy**
- **Antidepressant medication following same recommendations as for Major Depression**
 - Consider safety during breast feeding
- **Supplemental estradiol**

Estradiol for the Treatment of Postpartum Depression

- **23 women with the onset of Major Depression within 6 months postpartum**
- **Mean serum estradiol level = 22pg/ml**
- **Treated with 1mg sublingual micronized 17 β -estradiol 3-8 times/day (target estradiol level = 109)**
- **After week 1, mean serum estradiol level = 93pg/ml**
- **Mean MADRS scores decreased from 41 points at baseline to 11 points after one week of treatment**

Ahokas et al. J Clin Psychiatry. 2001; 62: 332-336

Bipolar Disorder Relapse During the Postpartum Period

- **33 to 50% of women with Bipolar Disorder have a postpartum relapse**
- **Postpartum Psychosis occurs in some relapses**
 - Distinguished from typical manic episode (eg. Delirium-like symptoms and confusion)
- **75% to 90% likelihood of recurrent episodes of puerperal psychosis following an index episode of puerperal psychosis**
- **Lithium may have prophylactic benefit against postpartum relapse in women with bipolar disorder**

Psychotropics and Breast Feeding

Psychotropic Medications During Breast Feeding

Class	Drug of Choice	Use with Caution	Avoid
Antidepressants	Sertraline	Fluoxetine Paroxetine	Newer Atypicals??
Mood Stabilizers	_____	Tegretol Depakote	Lithium
Antianxiety	Clonazepam Lorazepam	Other Benzodiazepine	_____
Sleep/Hypnotics	???	???	_____
Antipsychotics	???	Typicals Atypicals	_____

Ito, S. New Eng J Medicine. July 13, 2000: pg. 118-126 AND OTHERS

Perimenopause

Perimenopause

- **No standard definition**
- **Time of transition from regular menstrual cycles to complete cessation of menses**
- **Irregular menses or amenorrhea for ≤ 11 months**

Reliable Indicators of Perimenopause

- **Serum follicle-stimulating hormone (FSH) > 20 IU/L as measured on day 2 or 3 after onset of menses**
- **Reduced estradiol < 40 pg/ml as measured on day 2 or 3 after onset of menses**

Clinical Presentation of Perimenopause

- **Can resemble symptoms of a Major Depressive Episode**
 - Negative mood state
 - Sleep disturbance
 - Lack of concentration
 - Memory complaints
- **To diagnose a perimenopausal patient as having Major Depression, patient must meet DSM-IV criteria for severity, duration, significant impairment or distress**
- **History of depression is a risk factor for depressive symptoms during perimenopause**

Hormone Replacement Therapy (HRT) in the Perimenopause

- **HRT therapy should be considered in women**
 - Depressed mood without meeting criteria for a Major Depressive Episode
 - No past psychiatric history
 - Prominent vasomotor symptoms
 - Augmentation for partial response to antidepressant
 - Estrogen
 - Testosterone
 - Estrogen/Testosterone

Estradiol for Treatment of Perimenopausal Depression

- 50 perimenopausal women with depression
- 100ug transdermal 17B-estradiol vs. placebo
- 12 week randomized treatment phase

MADRS	Estradiol	Placebo	Remission	MADRS <10
Pre-Rx	24.6	21.8	Estradiol	68%
Post-RX	8.6	16.8	Placebo	20%

de Novaes Soares et al. Arch Gen Psychiatry. 2001; 58: 529-534

Menopause

Menopause

- **No menstruation for 12 consecutive months**
- **Estrogen levels drop 70-80%**
- **Testosterone levels also further decrease**
- **Higher than expected incidence of hypothyroidism**
- **Surgical menopause results in acute and significant drops in both estrogen and testosterone levels**

Depression in the Menopause

- **If criteria met for Major Depression:**
 - **SSRIs are first choice**
 - **Other antidepressants**
 - **May augment with estradiol**
 - **Psychotherapy**
- **If sub-clinical milder depression:**
 - **Consider Estrogen/Testosterone/Progesterone**
 - **Psychotherapy; group or individual**
 - **Nutritional supplements**