MENOPAUSE AND MENTAL HEALTH

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ROLE OF HORMONES

- **Estrogen and testosterone**
  - Mood altering and mood elevating

- **Testosterone**
  - Starts declining after the age of 25
  - Elderly men with very low levels of testosterone may have three times the risk of depression
ENDOGENOUS ESTROGENS

- Fluctuating levels
  - Puberty, PMS, breastfeeding, perimenopause

- Sudden drop in estrogen levels
  - Postpartum, abortion, ovarian cysts
  - Following ovulation, hysterectomy, oophorectomy

- Chronic low levels of estrogen
  - Postpartum, menopause, hysterectomy, oophorectomy
MENOPAUSE

- **Normal** process-physiologic, several years (30 year process from age 35-65)
- **Permanent cessation** of menstruation resulting from loss of ovarian follicular activity (WHO)
- **Twelve** months of amenorrhea with no identifiable cause
- Mean age 51.3 years
- Variety of symptoms may affect quality of life
- Estrogen replacement has been the mainstay of treatment for decades
FACTORS AFFECTING MENOPAUSE

- **Psychosocial**
  - Empty nest, cultural expectations, adjusting to changes in self

- **Domino**
  - Decreasing estrogen-hot flashes-depressed mood-insomnia, emotional and cognitive changes

- **Biochemical**
  - Declining estrogen-changes in serotonin, dopamine, NE, GABA
MENOPAUSAL TRANSITION

- Perimenopause or climacteric: 46-55
  - Serum *estrogen levels 300-500µ/ml* plummet down to *50-80 pg/ml*
  - Early- changes in the menstrual cycle of more than 7 days
  - Late-two or more cycles are skipped, and at least one interval of 60 days or more between cycles
  - 90% of women: irregular cycles-short, skipped, heavier, lighter
  - 10% of women: regular cycles, stop abruptly

- End point of transition is after 12 months of unexplained amenorrhea,-menopause

- Vasomotor symptoms, mood symptoms, cognitive problems
STRAW CRITERIA

• Stages of Reproductive Aging Workshop (STRAW)
  • American Society for Reproductive Medicine (ASRM)
  • National Institute on Aging (NIA)
  • National Institute of Child Health and Human Development (NICHD)
  • North American Menopause Society (NAMS)

• “The menopausal transition”

• Stages -5 to +2 –reproductive to menopausal transition to postmenopause
**STRAW CRITERIA**

Stages/Nomenclature of Normal Reproductive Aging in Women

Recommendations of Stages of Reproductive Aging Workshop (STRAW), Park City, Utah USA, July 2001

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<th>Stages:</th>
<th>-5</th>
<th>-4</th>
<th>-3</th>
<th>-2</th>
<th>-1</th>
<th>0</th>
<th>+1</th>
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<td>Terminology:</td>
<td>Reproductive</td>
<td>Menopausal Transition</td>
<td>Postmenopause</td>
<td></td>
<td></td>
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<tr>
<td>Early</td>
<td>Peak</td>
<td>Late</td>
<td>Early</td>
<td>Late *</td>
<td>Early *</td>
<td>Late</td>
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<table>
<thead>
<tr>
<th>Duration of Stage:</th>
<th>variable</th>
<th>variable</th>
<th>(a \leq 1) yr</th>
<th>(b \geq 4) yrs</th>
<th>until demise</th>
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<tr>
<td>Menstrual Cycles:</td>
<td>variable to regular</td>
<td>regular</td>
<td>variable cycle length (&gt;7 days different from normal)</td>
<td>(\geq 2) skipped cycles and an interval of amenorrhea (&gt;60 days)</td>
<td>none</td>
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<td>Endocrine:</td>
<td>normal FSH</td>
<td>(\uparrow) FSH</td>
<td>(\uparrow) FSH</td>
<td>(\uparrow) FSH</td>
<td>(\uparrow) FSH</td>
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*Stages most likely to be characterized by vasomotor symptoms \(\uparrow=\) elevated*
SYMPTOMS OF MENOPAUSE

- **Vasomotor symptoms (VMS):** hot flashes, night sweats and a lowered thermoneutral zone problems
- **Sleep problems:** sleep initiation, disrupted sleep due to multiple awakenings, sleep maintenance
- **Psychiatric symptoms:** depressed mood, anxiety, irritability
- **Vulvovaginal symptoms:** vaginal dryness, dyspareunia
- **Musculoskeletal symptoms:** aches and pains, joint stiffness and pain
- **Sexual concerns:** Decreased interest, decreased desire, external factors
VASOMOTOR SYMPTOMS

- **Hot flashes** - 80% of women, 10-20% have severe symptoms, 5-15 years, average age 51,
  - Mild 1-2/day
  - Moderate to severe - 6-10/daily, 6-10 minutes each
  - Anxious, nervous, irritable, or panic prior to the hot flash
  - Feeling hot out of the blue, followed by feeling chilled and shivering
  - Increase in blood flow to the skin, increase in sweating, skin temperature and conductance

- **Thermoneutral zone** – threshold between sweating and shivering
  - Narrowed in symptomatic
  - Absent in severely symptomatic women

- More common during the evening and night
MENOPAUSE AND MOOD DISORDERS

- Hot flashes, severe, persistent vasomotor-4.6 times greater risk of depression
- New onset depression-52% of women
- Past history of depression-4-9 times more likely to be depressed
- Prolonged perimenopause >27 months-increased risk of depression
- PMS, perinatal depression, OCP
- Surgical or premature menopause
- Negative or critical attitude towards aging and menopause
• Menopause transition-"window of vulnerability" for depression

• Harvard Moods and Cycles (HSMC) study-prospective assessment
  • Women with no history of depression-twofold increased risk

• Penn Ovarian Aging Study-prospective assessment
  • Fourfold increased risk for depressive and >twofold for MDD
  • Age, history of premenstrual symptoms, hot flashes, impaired sleep, race and employment status
  • Fluctuating hormone levels and not absolute hormone levels - trigger
ESTROGENS AND MOOD

• Estrogen (E) receptors are everywhere in the brain

• Mood, core body temperature, cognition
  • Hypothalamus, prefrontal cortex, hippocampus and brain stem

• Estrogen-increase in 5-HT and NE neurotransmission

• VMS: dysregulation of thermoregulatory center
  • Fluctuations in estrogen levels, increase NE tone in the hypothalamus
MANAGING MENOPAUSE

- Hormone replacement therapy
  - Estrogen, progestin, testosterone
- Psychotropics
  - SSRIs', SNRIs'
- Psychotherapy
  - CBT
- Non-pharmacologic interventions
  - Herbs
  - Yoga
HORMONES AND HOT FLASHES

- Estrogen was standard of treatment until 2002

- Women's Health Initiative: risks of estrogen

- Mild hot flashes: 1-3/day
  - Deep breathing, relaxation
  - Vitamin E 800 IU/day

- Moderate to severe hot flashes: 4-10/day
  - Estradiol 1 mg/day, decreases hot flashes by 80-90%
  - Estradiol plus progestin in women age 50-54 with moderate to severe vasomotor symptoms
    - Hot flashes decreased, sleep improved but mood did not improve
ESTROGEN AND MOOD

- **Estradiol-monotherapy in perimenopausal women with MDD**
  - As effective as antidepressants

- **Estradiol-monotherapy in postmenopausal women with MDD**
  - Not effective in treating depression

- Menopausal transition-"window of opportunity"-for estrogen therapy

- Antidepressant effects of estradiol persist even after 4 weeks of stopping it, whereas hot flashes and night sweats recurred
WOMEN'S HEALTH INITIATIVE (WHI)

- **10, 739** postmenopausal women, 50-79 years old, no uterus
  - Conjugated equine estrogens, unopposed 0.625 mg/day
  - Placebo
  - Average 6.8 years

- **16, 608** postmenopausal women, 50-79 years old- intact uterus
  - Combination HRT: conjugated equine estrogen 0.625 mg/day + medroxyprogesterone
  - Placebo
  - Average 5.6 year
WOMEN'S HEALTH INITIATIVE

- **Combination HRT**
  - ↑ risk of breast cancer, ischemic stroke, heart disease, blood clots
  - Stopping HRT: symptoms returned in more than half of the women

- **Unopposed estrogen or with a progestin**
  - Did not prevent cognitive decline in women 65-79
  - Slightly ↑ risk of probable dementia (WHI Memory Study)
  - HRT is not recommended for enhancing cognitive performance

- **FDA recommendation for HRT to manage menopausal symptoms**
  - Lowest effective dose for the shortest time needed
ESTROGEN ALONE STUDY

- **Strokes:** ↑ risk of both fatal and non-fatal strokes
- **Venous thrombosis:** ↑ risk
- Coronary heart disease: no significant difference in risk
- Colorectal or total cancer: no significant difference in risk
- Breast cancer: fewer cases, but not statistically significant
- Bone fractures: increased benefit-6 fewer hip fractures
- All deaths: no significant difference in risk
ESTROGEN+PROGESTIN STUDY

- 41% increase in strokes
- 29% increase in heart attacks, 22% increase in cardiovascular disease
- Doubling of rates of blood clots
- 26% increase in breast cancer
- 37% reduction in cases of colorectal cancer
- 1/3 reduction in rates of hip fracture rates, 24% reduction in total fractures
- No difference in total mortality (from all causes)
TYPES, ROUTES, AND DOSES OF ESTROGEN

- Conjugated oral estrogens, oral estradiol
- Oral or transdermal
  - Transdermal
    - Bypass the first-pass metabolism by the liver
    - Smokers
    - Preference
    - Less likely to cause blood clots, changes in breast density
- Low-dose, lower-dose, very-low-dose hormonal therapy
DOSING OF HORMONAL THERAPY FOR HOT FLASHES

- All women with **INTACT UTERUS** must take **COMBINATION HT**
  - Low-dose combination HT: lower risk of stroke, not sure if lower risk of breast cancer

- **ESTROGENS**: conjugated estrogen-Premarin (0.3mg, 0.625 mg, 0.9 mg, 1.25 mg, 2.5mg)
  - Conventional doses- 0.625mg Premarin
    - 75-90% reduction in hot flashes, 4 weeks to take maximal effect
  - Low-dose: 0.3mg Premarin
    - 65% reduction in hot flashes, 8-12 weeks to take effect
    - Not as effective in decreasing severity or frequency of hot flashes

- **PROGESTINS**:
  - Levonorgestrol IUCD: lower systemic levels of progestin, endometrial protection
  - Transdermal progesterone creams: no evidence of endometrial protection

- Stopping HT suddenly or gradually: no impact on return of symptoms
PSYCHOTROPICS FOR HOT FLASHES AND DEPRESSION

- **SSRIs**: 50% or more reduction in hot flashes and help depression
  - Paroxetine CR 12.5-25 mg/day
  - Citalopram 20-60 mg/day
  - Fluoxetine 20 mg/day
  - Escitalopram 5-20 mg/day
  - Sertraline 100 mg/day
PSYCHOTROPICS FOR HOT FLASHES AND DEPRESSION

- **SNRIs**: 60-70% reduction in hot flashes and also help mood symptoms
  - Venlafaxine 75-150 mg/day
  - Duloxetine 60-120 mg/day
  - Mirtazapine 30-60 mg for severe depression and as an adjunct to estrogen

- **Gabapentin 900 mg/day**: for vasomotor symptoms

- **Hot flashes + moderate to severe depression**
  - SNRI or SSRI first line
TESTOSTERONE IN WOMEN

- Responsible for libido in men and women
  - Lower levels in women between the ages of 20-50
  - OCP’s, lactation, anorexia

- Total hysterectomy with bilateral oophorectomy
  - Sudden loss of 50% testosterone and 80% estradiol

- Increasing reports of low libido with increasing age until menopause
  - 30% at age 30, 50% at age 50, 27% in women 50-59

- Post natural menopause, most women have adequate levels of testosterone, to sustain their libido

- Luteinizing hormone stimulates ovarian cells to produce androgens
FEMALE ANDROGEN DEFICIENCY SYNDROME (FADS)

- Thinning pubic and axillary hair, decreased body odor, lethargy, don’t feel well
- Depressed mood, decreased libido
- Estrogen levels are adequate, low testosterone and DHEA
- Replace testosterone to help with the above
- Also helps with bone and muscle stimulation
- Helps decrease hot flashes
RISKS OF TESTOSTERONE REPLACEMENT THERAPY

- ↓ HDL levels
- History of heart disease, HDL <45 mg/dl-consult a cardiologist
- Darkening and thickening of facial hair
- High energy levels, irritability
- Aggressive, argumentative behaviors
- Need more studies for effects on long term use
SWAN STUDY

• Study of Women’s Health Across the Nation (SWAN)-1994, ongoing
  • Multi-site, longitudinal, epidemiologic study of health of women in their middle years
  • Physical, biological, psychological and social changes
  • Understand how life experiences impact health and quality of life as we age
  • National Institute on Aging (NIA)
  • National Institute of Nursing Research (NINR)
  • National Institute of Health (NIH)
  • Office of Research on Women’s Health
  • National Center for Complementary and Alternative Medicine
  • 3,302 participants form seven centers: MI, MA, IL, CA, NJ, PA
  • Five racial /ethnic groups, various cultures and backgrounds
NON-PHARMACOLOGIC MANAGEMENT OF HOT FLASHES

- **Environmental**: layers of light clothing, fans, lower thermostats

- **Exercise**: fewer reports of hot flashes by physically active women
  - Not effective in decreasing hot flashes, may actually increase the frequency

- **Paced respiration**: slow, deliberate deep breathing that is sustained for a specific period of time
  - 6-8 breaths per minute, practice for 15 minutes twice a day, apply the breathing with each hot flash
  - Healthy peri and post-menopausal women
  - Decrease frequency and severity of hot flashes
  - Need more studies-RCT
NON-PHARMACOLOGIC MANAGEMENT OF HOT FLASHES AND MENOPAUSE

- **CBT: pilot study Green et al**- two 10 week pilot groups with four participants each
  - Decrease in severity and frequency of hot flashes, depression, anxiety and improvement in quality of life

- **Three RCT's >600 women**
  - Peri- and postmenopausal women, menopausal symptoms caused or worsened by breast cancer treatments
  - Self help CBT-book and CD or 8 hours of group CBT-group was more effective
  - Helped improve sleep, mood and hot flashes and night sweats
YOGA AND MENOPAUSE

• Complementary health approach to quality of life
• Community based study in Tamil Nadu, India
• 260 menopausal women, divided equally into study and control groups
• 18 weeks of yoga practice
• "Enjoy menopause and experience the freedom, liberation, and energy that it brings."
HERBS AND HOT FLASHES

• BLACK COHOSH
  • May help, six trials, methodological problems, consistent results
  • Isolated case reports of hepatotoxicity

• VITAMIN E, DONG QUAI, EVENING PRIMROSE OIL- not effective

• PHYTOESTROGENS

• Drug-herb interactions
PHYTOESTROGENS

- Plant derived products, found in soy and other food, dietary supplements
  - Marketed as a natural alternative for ERT
  - Soy infant formula, soy protein in many processed foods
  - Berries, legumes, soybeans, flaxseeds, grains, nuts and fruits

- Asians consume a soy rich diet
  - Lower rates of heart disease, menopausal symptoms, breast cancer, other hormone dependent cancers, obesity, diabetes

- Weak estrogen agonists/antagonists-endocrine disruptors
  - Adverse health effects
ENDOCRINE DISRUPTING COMPOUNDS- EDCs

- SYNTHETIC OR MAN MADE EDCs
  - Pesticides- DDT, methoxychlor
  - Industrial lubricants-PCBs
  - Plasticizers-phthalates, bisphenol A (BPA)

- Increasing risk of obesity, cancer and declining reproductive health

- Phytoestrogens behave similarly to EDCs on many cellular and molecular targets
  - Favorable versus concern
SOY DIET IN ASIANS AND CAUCASIANS

- **Asians: long time, no consequences**
  - High consumption throughout life
  - Low to none during breast feeding
  - Tofu, tempeh, unprocessed
  - More seafood and less animal fat

- **Caucasians**
  - High consumptions in infants in the first year of life and then low to none
  - More animal fats
HEALTH BENEFITS OF PHYTOESTROGENS IN HUMANS

• Phytoestrogens in menopause: “Soy may bring relief”
  • Most studies have showed minimal or no benefit
  • Insufficient evidence to support or reject the use of soy foods and isoflavone supplements (soy or red clover), black cohosh, vitamin E

• Phytoestrogens in prevention of osteoporosis
  • Inconsistent results, depends on the dose, duration and the age of the person
  • Depends on the ability of the bio to convert to “equol”
HEALTH BENEFITS OF PHYTOESTROGENS IN HUMANS

- Phytoestrogens in the prevention of heart disease
  - Marginal benefits on lowering LDL, who replace a portion of animal protein in their diet with soy

- Phytoestrogens and risk of breast cancer
  - No clear consensus, no clear recommendations
  - Women with no serious risk factors for breast cancer and no family history may include soy in their diet
HEALTH RISKS OF PHYTOESTROGENS IN HUMANS

- Retrospective cohort study 952 women
  - 248 women: fed infant based soy formula
  - 563 women: non soy-based formula
  - Longer menstrual bleeding and discomfort

- Sister study: 19,000
  - Consumption of soy linked with increased risk of developing fibroids
HEALTH RISKS OF PHYTOESTROGENS IN HUMANS

- Phytoestrogens in the reproductive tract
- 2008 SUNY Downstate Medical Center: 3 women-35-56: clinical case report, need more studies
  - Dysmenorrhea, abnormal bleeding, endometrial pathology
  - Soy diet reduced/eliminated: symptoms got better
  - Youngest of the three on soy-rich diet since age 14-secondary infertility-decreased soy consumption-got pregnant
  - Oldest of the three-estimated >40 gm of isoflavone intake per day
- Soy foods should be used with caution in women trying to get pregnant or have irregular menstrual cycles
DIETHYLSTILBESTROL (DES)

- Synthetic estrogen: 1938-1971: 10 million women
- Believed to reduce risk of miscarriage, routine prophylactic for all pregnant women, with no regard to history of miscarriage
- Non-medical uses of DES in lower doses: lotions, shampoo and growth enhancers for chicken and cattle
- First report of adverse effects in 1971
DIETHYLSTILBESTROL (DES)

- DES daughters: DES exposure in utero
  - Extremely rare form of vaginal clear cell carcinoma
    - At a much earlier age
    - More frequently than in unexposed women
  - Vaginal dysplasia, vaginal and/or cervical adenosis
  - Malformations of the uterus, cervix and vagina
  - Lower sperm count, undescended testes, increased risk of testicular cancer
  - Infertility, late spontaneous abortion, preterm delivery
PHYTOESTROGENS

- "Critical windows of exposure": when trying to predict effects of taking endocrine disruptors such as phytoestrogens
- Be careful in using soy infant formula
- Need studies
- Fetal DES exposure adverse effects were predicted or replicated in animal studies
SOY–BASED INFANT FORMULAS

• Babies with cow milk allergy, colic
  • Popular, vegetarian, thought to be healthier
  • 25% of 1 million US infants, raised on soy-based formula

• Isoflavones cross the placenta barrier- cord blood, amniotic fluid
  • Higher blood levels in infants exclusively fed soy formula

• Higher content in soy infant formula than other foods
  • 0.3-1.2 mg/kg/day-Asians-soy –based diet
  • 6-9 mg/kg/day-infants on soy formula-isoflavones
  • 7 times >FDA recommendation for adults
SOY-BASED INFANT FORMULAS IN BPA FREE BOTTLES

- 1000 ng/ml- circulating phytoestrogen concentrations
  - 13,000-22,000 times > own endogenous estrogen levels
  - 50-100 times > estradiol levels in pregnant women
  - 3000 times > estradiol levels during ovulation
  - Levels higher than those reported for BPA and phthalates

- Estrogenized vaginal epithelium-female infants on soy formula
  - None in infants fed cow milk or breast fed

- Need to determine if soy formula is safe in the long term

- "Absence of evidence is not an evidence of absence"
NATURAL DOES NOT NECESSARILY MEAN SAFE

• Phytoestrogens are endocrine disruptors
  • Similar to synthetic industrial, household products
  • We love soy, hate these chemicals
  • Benefits of soy are exaggerated, while the adverse effects underappreciated

• AAP in 2008
  • "Isolated soy protein-based formula has no advantage over cow milk-protein based formula
  • Soy formula has "no proven value in the prevention or management of infantile colic or fussiness."
  • Did not recommend against its use

• UK, Australia, New Zealand recommend against indiscriminate use
WHEN TO CONSIDER HRT

- **Menopausal status**
  - Effective for depression in menopausal transition but not postmenopause
  - Intact versus absent uterus—combination HRT versus estrogen alone

- **Timing of onset of depressive symptoms**
  - With the onset of menstrual irregularity, hormonally related

- **History of mood disorders in the reproductive age**
  - PMDD, postpartum depression—fluctuations in ovarian hormones, sensitivity

- **Medical history**: increase risk of cancers or recurrences of cancers (breast, endometrial), blood clots

- **Choice of the patient**
WHEN TO CONSIDER ANTIDEPRESSANTS

- **SSRIs, SNRIs**
  - Hot flashes and depression
  - May use in conjunction with hormones
CONCLUSIONS

- Menopausal transition and menopause are normal processes
- Multifactorial and maybe over-pathologized
- Multiple options for treatment
- Assess risks and benefits of each, obtain informed consent
REFERENCES


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