MENOPAUSE AND MENTAL HEALTH
ANUPAMA D. YEDLA, M.D.
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 and then 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
- Vasomotor symptoms, mood symptoms, cognitive problems
STAGES OF MENOPAUSE

- Early menopause: 35-45
- Low inhibin-increase FSH-more estrogen-endometrial thickening and risk of fibroids
- Higher FSH-higher activin-faster egg development-faster egg depletion
- Menses are generally normal
- Serum estrogen levels 100/pg/ml
LATE MENOPAUSE

- Age 55 and older
- No more eggs or follicles
- Amenorrhea for at least 12 months
- Estrogen and androgen deficiency, but levels are stable
- Vaginal dryness, night sweats, hot flashes, sleep issues, fatigue
- Thinning body hair, thinning and wrinkled skin
- Decreased body odor, decreased bone density
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
### Stages/Nomenclature of Normal Reproductive Aging in Women

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

<table>
<thead>
<tr>
<th>Stages:</th>
<th>-5</th>
<th>-4</th>
<th>-3</th>
<th>-2</th>
<th>-1</th>
<th>0</th>
<th>+1</th>
<th>+2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminology:</td>
<td>Reproductive</td>
<td>Menopausal Transition</td>
<td>Postmenopause</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>Peak</td>
<td>Late</td>
<td>Early</td>
<td>Late*</td>
<td>Early*</td>
<td>Late</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of Stage:</td>
<td>variable</td>
<td>variable</td>
<td>a 1 yr</td>
<td>b 4 yrs</td>
<td>until demise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menstrual Cycles:</td>
<td>variable to regular</td>
<td>regular</td>
<td>variable cycle length (≥7 days different from normal)</td>
<td>≥2 skipped cycles and an interval of amenorrhea (≥60 days)</td>
<td>none</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocrine:</td>
<td>normal FSH</td>
<td>↑FSH</td>
<td>↑FSH</td>
<td>↑FSH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Stages most likely to be characterized by vasomotor symptoms ↑ = 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
- More common during the evening and night
MENOPAUSE AND MOOD

- 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 AND MOOD

- 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'

- Nonpharmacologic
  - Herbs
  - Yoga

- Psychotherapy
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)

<table>
<thead>
<tr>
<th>Group</th>
<th>Participants</th>
<th>Age Range</th>
<th>Hormone Treatment</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenopausal women with no uterus</td>
<td>10,739</td>
<td>50-79</td>
<td>Conjugated equine estrogens, unopposed 0.625 mg/day</td>
<td>6.8 years</td>
</tr>
<tr>
<td>Postmenopausal women with intact uterus</td>
<td>16,608</td>
<td>50-79</td>
<td>Combination HRT: conjugated equine estrogen 0.625 mg/day+medroxyprogesterone</td>
<td>5.6 years</td>
</tr>
</tbody>
</table>
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
SUMMARY OF FINDINGS OF 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
SUMMARY OF FINDINGS FOR THE ESTROGEN PLUS 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
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)
  - 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
SWAN STUDY

• 1994, now ongoing for 22 years
• 3,302 participants from seven centers: MI, MA, IL, CA, NJ, PA
• Five racial/ethnic groups, various cultures and backgrounds
NON-PHARMACOLOGIC MANAGEMENT OF HOT FLASHES AND MENOPAUSE

• 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 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
DIETHYLYSTILBESTROL (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
CONCLUSIONS-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
• Work closely with gynecologists if necessary
REFERENCES


