Hormone Replacement Therapy

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What is Menopause?

- Cessation of menstruation as a result of the aging process of or surgical removal of the ovaries; change from fertility to infertility.
- Physiological changes that take place within women between the ages of 30 to 60.
- Hormone levels change in female body; practically the production of estrogen.
- Perimenopause and menopause can last 10 plus years.
- Menopause itself begins 12 months after a woman's final period.

Stages of Menopause

- **Perimenopause**
  - Irregular, short menstrual periods
  - Uncomfortable symptoms include hot flashes, insomnia, irritability, and backaches
  - May last four to five years or longer
- **Menopause**
  - 12 months after the last menstrual period
  - Production of progesterone and eggs stops
  - Normally happens between the ages of 45 and 55
- **Postmenopause**

Symptoms

- Irregular menstrual periods
- Hot flashes
- Irritability, depression, anxiety
- Insomnia, poor sleep quality
- Palpitations, night sweats
- Forgetfulness (in some women)
- Vaginal dryness
- Headaches, vaginal infections, joint aches and pains

Treatment of Menopause

- Hormonal Replacement Therapy
- Non-hormonal therapy
  - SERM
  - Bisphosphonate

Hormonal Replacement Therapy

- Benefit of HRT
  - Relief of Symptoms
  - Preventive Therapy

Hormonal Replacement Therapy

- Benefit of HRT for Relief of Symptoms
  - Hot flashes
    - Highly effective
    - Usually required for a relatively short period of time, e.g. 1 to 3 years
  - Mood disturbance
    - Improve irritability and anxiety in many menopausal women
    - Relieve mild depressive symptoms
    - Mechanism not sure, ? direct effect vs secondary to alleviation of physical symptoms

Hormonal Replacement Therapy

- Benefit of HRT for Relief of Symptoms
  - Urogenital symptoms
    - Improve urogenital atrophy, thinning, dryness and loss of elasticity
    - Relieve symptoms of dyspareunia
    - Improve sexual functioning and sexuality
    - Contradictory data on incontinence
      - Some studies indicate that HRT may relieve symptoms of urinary urgency, urge incontinence, stress incontinence, frequency and dysuria, but some data showed negative effects

Hormonal Replacement Therapy

- Benefit of HRT for Preventive Therapy
  - Coronary disease
    - Primary and Secondary Prevention of IHD was previously demonstrated by nonrandomized, observational studies
    - Until June 2002, there is no randomized, observational studies on primary prevention of IHD
    - However, new data concerning prevention of IHD (primary and secondary) come up recently …

Hormonal Replacement Therapy

- HERS Study
  - Heart and Estrogen/Progesterone Replacement Study
  - Currently the only randomized, placebo-controlled trial of the HRT for *secondary prevention*
  - 2763 post-menopausal women with IHD, average age 67 years, received HRT (estrogen + progesterone) was followed up for 4.1 years.
  - Risk of MI increased during the first year, although risk seemed to decreased during the remainder of the study.

JAMA. 1998;280:605-613

Hormonal Replacement Therapy

- HERS II Study
  - Follow-up open-label study of HERS, lasting for 2.7 years
  - Designed to evaluate the effects of longer-duration of HRT
  - Initial trend from HERS suggesting a reduced risk of MI with longer duration of HRT did not persist with additional follow up period
- Combining HERS and HERS II Studies
  - There was no risk reduction from HRT during almost 7 years.

JAMA. 2002;288(1):49-57,58-66,99-101

Hormonal Replacement Therapy

- Anything even newer ?
- Read the newspaper or journals recently ?
- To be continued …

Hormonal Replacement Therapy

- Benefit of HRT for Preventive Therapy
  - Coronary disease
    - Current evidence is not sufficient to recommend HRT for cardiovascular indication for most women at risk of IHD
    - Instead, aggressive risk factor modification is recommended.
    - Also, there is no evidence that IHD or the presence of cardiac risk factors is a contraindication to HRT

Hormonal Replacement Therapy

- Benefit of HRT for Preventive Therapy
  - Osteoporosis
    - Prevention and treatment of osteoporosis are well documented and widely accepted use of HRT
    - Beneficial effect of HRT on bone mineral density is well proven
    - Trials
      - No randomized prospective trial for hip fracture
      - Large case-controlled studies showed HRT can prevent vertebral fracture
      - A multicenter clinical trial sponsored by the Women's Health Initiative, focusing on the effect of HRT on fracture risk, is currently underway and data will be available by 2006.

Hormonal Replacement Therapy

- Benefit of HRT for Preventive Therapy
  - Alzheimer's Disease and Cognitive Functioning
    - HRT may improve some aspects of cognitive functioning
    - Long term HRT may : -
      - Reduce the risk of Alzheimer's disease
      - Slow the progression and improve cognitive functioning and mood in elderly women with established Alzheimer's disease.

Hormonal Replacement Therapy

- Benefit of HRT for Preventive Therapy
  - Colon Cancer
    - The protective benefit is suggestive but not proven
    - Long-term use solely for this purpose is NOT recommended
  - Skin / Wound Healing
    - Beneficial effect on collagen metabolism, improve skin tone and wound healing
  - Tooth loss
    - Reduce maxillary and mandibular osteoporosis and prevent resulting tooth loss
  - Macular degeneration
    - Recent date suggests a decreased incidence of macular degeneration in women on HRT

Risk of HRT

- Breast Cancer
  - Real controversy !!!
  - Among the 55 studies published between 1974-1996, 90% failed to demonstrate an increased risk.
  - Meta-analysis in 1997 by the Oxford Group
    - The findings of increased breast cancer in HRT user may not be conclusive and may be open to questions of statistical inaccuracy.

Risk of HRT

- Breast Cancer - some acceptable findings
  - Small increase (up to 1.3x) in breast cancer risk after 5-15 years or more of HRT (i.e. use HRT < 5 years is safe)
  - Breast cancer *motality does not increased* with HRT because the cancer tends to be less advance, lower rate of node positivity, better differentiated and more favorable histological type.
  - Risk of breast cancer is increase in CURRENT USER only. Previous use of HRT carry no increase risk.

Risk of HRT

- Endometrial Cancer
  - Increased only in women taking unopposed estrogen
  - Post-hysterectomy patient can take unopposed estrogen without any increase in risk.
- Gallbladder Disease
  - The risk of gallbladder disease continues at higher, premenopausal level in women taking HRT
- Venous Thrombosis
  - Risk increased up to 3-folds in CURRENT user only
  - Absolute risk of still relatively low, i.e. increase from approx 10 cases per 100,000 women in general population to approx 30 cases per 100,000 women on HRT.
- Ovarian cancer
  - May be a week association but not proven at this time.

Contraindication

- Absolute contraindication
  - Prior history or existing breast cancer
  - Prior history or existing endometrial cancer
  - Prior history of venous thrombosis
  - Undiagnosed abnormal vaginal bleeding
  - Severe, active liver disease with abnormal LFT
- Relative contraindication
  - Family history of breast cancer
  - Hyper-TG
  - Gallstone and gallbladder disease

Contraindication

- The following are currently NOT contraindicated
  - HT
  - Smoking
  - Obesity
  - Migraine headache
  - Uterine fibroid
  - Endometriosis
  - Fibrocystic breast change

Pre-treatment Assessment

- History
  - General health
  - Perimenopausal symptoms
  - Gynecological history (e.g. endometrial cancer)
  - Risk of osteoporosis and CVS disease
- Physical Examination
  - Complete physical examination
  - Pelvic examination
  - Pap smear

Pre-treatment Assessment

- Optional investigation
  - FSH - if symptoms of menopause is atypical
  - Mammogram - if patient is at risk of CA breast
  - Bone densitometry (e.g. DEXA scan)
  - Pelvic USG / Abdominal USG
  - Lipid profile and FBS
  - LFT
  - Endometrial aspiration

Follow-up Plan

- Follow up at 3rd, 6th and 12th month for
  - Symptom control
  - Compliance, side-effects and bleeding pattern
  - Urine multistix
  - BP measurement
- Other investigation
  - Yearly physical examination + cervical smear
  - 2-yearly mammogram
  - Blood test, endometrial aspiration and bone densitometry when indicated

HRT Regimen

- Patient with Hysterectomy done
  - First Line
    - Unopposed estrogen therapy
    - Examples
      - conjugated estrogen 0.625 mg Daily
      - estradial 2 mg Daily
  - Second Line
    - Non-oral estrogen
      - Transdermal patch (e.g. Estraderm)

HRT Regimen

- Intact uterus & amenorrhoea < 2 year
  - First Line
    - Sequential combined therapy
      - Estrogen is given continuously with sequential addition of progesterone for 10 to 14 days
      - Example 1 -
        - 14 conjugated estrogen 0.625 mg
        - 14 - conjugated estrogen 0.625 mg + medroxyprogesteron 5 mg
      - Example 2 -
        - 12 - estradiol 2 mg
        - 10 - estradiol 2 mg + norethindrone 1 mg
        - 6 - estradiol 1 mg

HRT Regimen

- Intact uterus & amenorrhoea < 2 year
  - Second Line
    - Cyclic estrogen + cyclic progesterone
      - Prempak (28-day cycle)
        - Day 5 to 25 - conjugated estrogen 0.625 mg Daily
        - Day 12 to 21 - add medrogesteron 5 mg Daily
        - Day 26 to 4 - pill free
        - In the absence of menstruation, administration is started arbitrarily.
  - Predictable monthly withdrawal bleeding is expected, and some women may achieve amenorrhoea eventually.

HRT Regimen

- Intact uterus & amenorrhoea > 2 year
  - First Line
    - Continuous combined therapy
      - Very little endometrial stimulation, therefore no withdrawal bleeding in most women (but 5-15% women may have unpredictable spotting indefinitely)
      - Example 1 -
        - conjugated estrogen 0.625 mg
        - medroxyprogesteron 2.5 mg
      - Example 2 -
        - estradiol 2 mg
        - norethisteron 1 mg

HRT Regimen

- Intact uterus & amenorrhoea > 2 year
  - Second Line
    - Tibolone 2.5 mg daily
      - C-19 steroid
      - Estrogenic + progesteogenic + weak androgenic properties
      - No withdrawal bleeding
      - Beneficial effects
        - symptoms + prevent bone loss
        - improve lipid profile
        - libido stimulation
      - An alternative in women who have relative contraindication to estrogen
      - Substantial risk of breakthrough bleeding, therefore recommended to start therapy not earlier than one year after menopause to minimize breakthrough bleeding

Non-hormonal Therapies

- Selective Estrogen Receptor Modulators (SERMs)
  - SERMs bind to all estrogen receptors but have different effects in various tissues
  - Raloxifene
    - First SERM to be approved by the FDA (now the only one)
    - Bind to estrogen receptor in bone and therefore improve bone mineral density, biochemical markers of bone turnover.
    - Also improve serum lipid profiles and can possibly prevent IHD (NOT PROVEN)

Non-hormonal Therapies

- On the other hand, Raloxifen DOES NOT
  - Increase risk of breast cancer (may even protect)
  - Treat hot flashes (may make them worse)
  - Relieve symptoms of vaginal atrophy
  - Appear to stimulate the endometrium
- Current indication – prevent and treatment of osteoporosis
- Contraindications
  - Premenopausal or perimenopausal (worsen symptoms)
  - History of thromboembolism
- Possible Side Effects
  - Hot flashes and leg cramp
  - NO breast pain or breast enlargement
- Dosage - Raloxife 60mg daily (any time of the day, with or w/o meal)

Non-hormonal Therapies

- Bisphosphonates
  - FDA-approved for prevention and treatment of osteoporosis
  - Prevention
    - Alendronate 5 mg daily
    - Residronate 5 mg daily
  - Treatment
    - Alendronate 10 mg daily (or 70mg once weekly preparation)
    - Residronate 5 mg dailyl
  - Side Effect – Esophagitis
    - Women with pre-existing esophageal disease may not tolerate
    - Special precaution in drug intake (alendronate)

Summary

- Women with menopausal symptoms
  - Exclude contraindication
  - Taking the new studies (HERS and WHI) into consideration, short-term use still has risk of coronary heart disease and thromboembolic disease.
  - Discuss with patient and balance the risk against the severity of symptoms.
  - Consider to start HRT for 1 to 5 years and stop.

Summary

- Women with increased risk of osteoporosis
  - Exclude contraindication of HRT $\longrightarrow$ consider HRT
  - Also explain other treatment options available (e.g. SERM, alendronate, etc)
  - Duration of Treatment
    - HRT – may be continued indefinitely, bone loss recur once HRT was stopped
    - Alendronate – therapeutic efficacy has been deomonstrated for 7 years. Safety and efficacy beyond 7 years have not yet been established. No accelerated bone loss observed after discontinuation.
    - Risedronate – therapeutic efficacy and safety had been demonstrated for a 3-year period only.
    - SERM – Efficacy and safety have ben demonstrated for up to 40 months.

Summary

- Women who start HRT for preventive therapy
  - Think twice !
  - May experts (including those from WHI) advise primary care doctor to STOP prescribing HRT for this purpose.