Menopause and Hormone Replacement Therapy

Daniel Breitkopf, MD
Department of Obstetrics and Gynecology
University of Texas Medical Branch
Galveston, Texas USA
Objectives

- Define the indications and contraindications for HRT
- Describe the HRT regimens in use today and their clinical usage
- Describe the management of bleeding irregularities on HRT
  - When to do an endometrial biopsy
  - When to order an ultrasound/sonohysterogram
Menopause

- At birth, the female has 1-2 million oocytes
- By puberty, only 440,000 oocytes remain
- By age 30-35 the number has dropped to 100,000
- Follicular maturation is induced by the pituitary release of Follicle Stimulating Hormone (FSH)
Menopause

- With advancing age, the remaining oocytes become increasingly resistant to FSH
- FSH gradually rises until menopause when it is usually greater than 30 mIU/ml
Menopause

- Menopause is defined as the absence of menstrual periods for at least 6 months in a woman over 40
- In the USA, the average age of a woman at menopause is 51
- 1% of women will undergo menopause before age 40
- Women who smoke cigarettes and who are malnourished will have earlier menopause
Menopause-Symptoms

- First symptoms are often menstrual irregularities
  - Menstrual cycles shorten or lengthen
- Hot flushes and vasomotor instability
  - sudden sensation of warmth, skin of face and chest will become flushed
  - then patient will experience a chill
  - this is the result of lower estrogen levels
  - more bothersome at night
Menopause-Symptoms

• Sleep disturbance
  – The time it takes to fall asleep is longer than when the woman was younger
  – Total length of time asleep is shorter

• Vaginal dryness/genital tract atrophy
  – vaginal mucosa and endometrium become thin and dry
  – irritation, difficulty with sexual intercourse may develop
Menopause-Symptoms

• Mood changes
  – Depression, crying spells may develop

• Skin and nails
  – skin and nails become thinner

• Osteoporosis
  – Bone density is lost at a rate of 1-2% per year after menopause
  – Risk of hip and vertebral fracture increases as soon as 5 years after menopause
Menopause-Symptoms

• Cardiovascular Lipid changes
  – Total cholesterol increases, high density lipoprotein (HDL) cholesterol decreases, and low density lipoprotein increases
  – Risk of heart attack and stroke increases in women after menopause
Menopause Diagnosis

- Use symptoms and signs
- Do not depend upon FSH
- FSH will often not rise until late in the perimenopausal period and may fluctuate
- Normal FSH does not exclude the perimenopause
- Consider thyroid disease if FSH is normal
- No need for biopsy prior to starting HRT
Menopause-Therapy

• For asymptomatic women, no therapy or treatment is necessary
  – Calcium intake should be at least 1500 milligrams a day
  – Weight bearing exercise will help in preventing osteoporosis

• For symptomatic women or for prevention of osteoporosis and heart disease, hormonal therapy is useful
Hormone Replacement Therapy (HRT)
Indications/Contraindications

• Indications
  – Relief of menopausal symptoms
    • Hot flashes, mood irritability, vaginal dryness, loss of libido
  – Osteoporosis prevention
  – Modify risk of heart attack, stroke

• Contraindications
  – Undiagnosed abnormal genital bleeding
  – Estrogen dependent neoplasia (Breast, Uterus)
  – History of thromboembolism, stroke
  – Liver dysfunction/disease
HRT Regimens

- Unopposed estrogen is associated with endometrial hyperplasia and carcinoma
- Progesterone withdrawal required at a minimum of every three months
- In last five years continuous suppression of the endometrium with combined therapy has become popular
HRT Regimens-cyclic

- Cyclic regimens
  - Conjugated estrogens (Premarin) 0.625 mg + MPA (Provera) 10 mg, 10 days every month
  - May substitute esterified estrogen
  - May use other progestins
    - Norethindrone (Aygestin) 5 mg
    - Norethindrone 0.7 mg (0.35 mg in minipill)
    - Megesterol (Megace) 20 mg
    - Micronized progesterone (Prometrium) 100 mg
HRT Regimens - cyclic

• Oral contraceptives
  – use of newer 20 microgram pills
    • 0.625 mg conjugated estrogens = 5 micrograms of ethinyl estradiol
  – May have hot flashes during hormone free interval
  – Better control of bleeding in younger patients
HRT Regimens-cyclic

- Advantage to cyclic regimen is that bleeding is predictable and controlled
- Will usually have withdrawal periods (80-90%), while bleeding is less with continuous regimens
- Better for younger patients (<50) because of better cycle control
HRT Regimens-continuous

- Premarin (conjugated estrogens) 0.625 mg/Provera (medroxyprogesterone) 2.5 mg
- Premarin 0.625 mg/Provera 5 mg
- Advantages: compliance, induction of amenorrhea
- Disadvantages: irregular bleeding/spotting
  - 40-60% will have breakthrough bleeding in first 6 months
  - 20% will have breakthrough bleeding after one year
Selection of regimen

- If bleeding is heavy and irregular, try cyclic regimen first for cycle control
  - May try switch to continuous after one year
- Younger women tend to have less irregular bleeding with cyclic regimens
- Continuous better for women who are amenorrheic or older than 50
- Younger women, surgically menopausal tend to need more estrogen at first-may need to titrate dose/schedule
Addition of Androgen

- Use of testosterone supplements
- Postmenopausal ovary does produce testosterone
- Supplementation may improve libido and hot flashes
- Adverse effect on lipid profile
Side effect management

• Progestin problems: bloating, breast tenderness, mood alteration
  – try another formulation first
  – combination patch
• GI upset-nausea
  – decrease estrogen dose (can go as low as Premarin 0.3 mg)
  – use estrogen patches
Management of bleeding

• Expect some irregular spotting for the first three months, especially with continuous progestins
  – if persists can try increasing progestin dose or switching to cyclic regimen
  – Investigate irregular bleeding if it occurs after the first 6 months

• Always need to evaluate unscheduled bleeding on cyclic regimens
  – Withdrawal bleed should occur at the end or after the progestin is administered
Bleeding on HRT-evaluation

• What test should be performed on the patent with persistent irregular bleeding on HRT?

• What you are trying to rule in or out?
Postmenopausal Bleeding

• Etiologies:
  – Atrophic Endometritis: 30%
  – Endometrial Polyps: 10%
  – Submucosal Fibroids: 10%
  – Endometrial Hyperplasia: 10%
  – Uterine Malignancy: 10%
  – Miscellaneous: 30%
Postmenopausal Bleeding

• Workup
  – Endometrial biopsy
  – If Endometrial biopsy negative, observation
  – If persistent, then Dilation & Curettage
  – Hysteroscopy as adjunct to Dilation & Curettage
Evaluation of irregular bleeding on HRT

• Etiology
  – Hormonal-breakthrough bleeding, inadequate progesterone
  – Structural-Polyps, myomas
  – Neoplasia-hyperplasia, carcinoma

• Endometrial biopsy is the standard test for any abnormal bleeding
  – very sensitive for neoplasia
  – not sensitive for polyps, fibroids
Evaluation of irregular bleeding on HRT

• Ultrasound
  – Transvaginal ultrasound allows for high resolution imaging of the endometrium
  – Normal is less than 5 millimeters by most studies
  – Stripe of greater than 5 millimeters requires further evaluation
  – If EMB is negative, can use sonohysterography or hysteroscopy for further evaluation
  – Many patients with negative EMB and thickened EMS will have polyps
Sonohysterography

- Saline infusion via trans-cervical catheter while performing ultrasound
- Helps to evaluate abnormally thickened endometrial stripe
- Polyps and fibroids visualized easily
- Focal thickening of stripe can be seen indicative of hyperplasia/carcinoma
## Triage of Postmenopausal Bleeding

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N=92

O’Connell, AJOG, 1998
TRIAGE OF POSTMENOPAUSAL BLEEDING

ENDOMETRIAL BIOPSY

AdenoCA, Hyperplasia
Operative Mgmt

Atrophy, Insufficient, Polyp

SHG

Intracavitary Mass
Continued Bleeding

Negative
No Bleeding

O’Connell, AJOG, 1988