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 staring 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

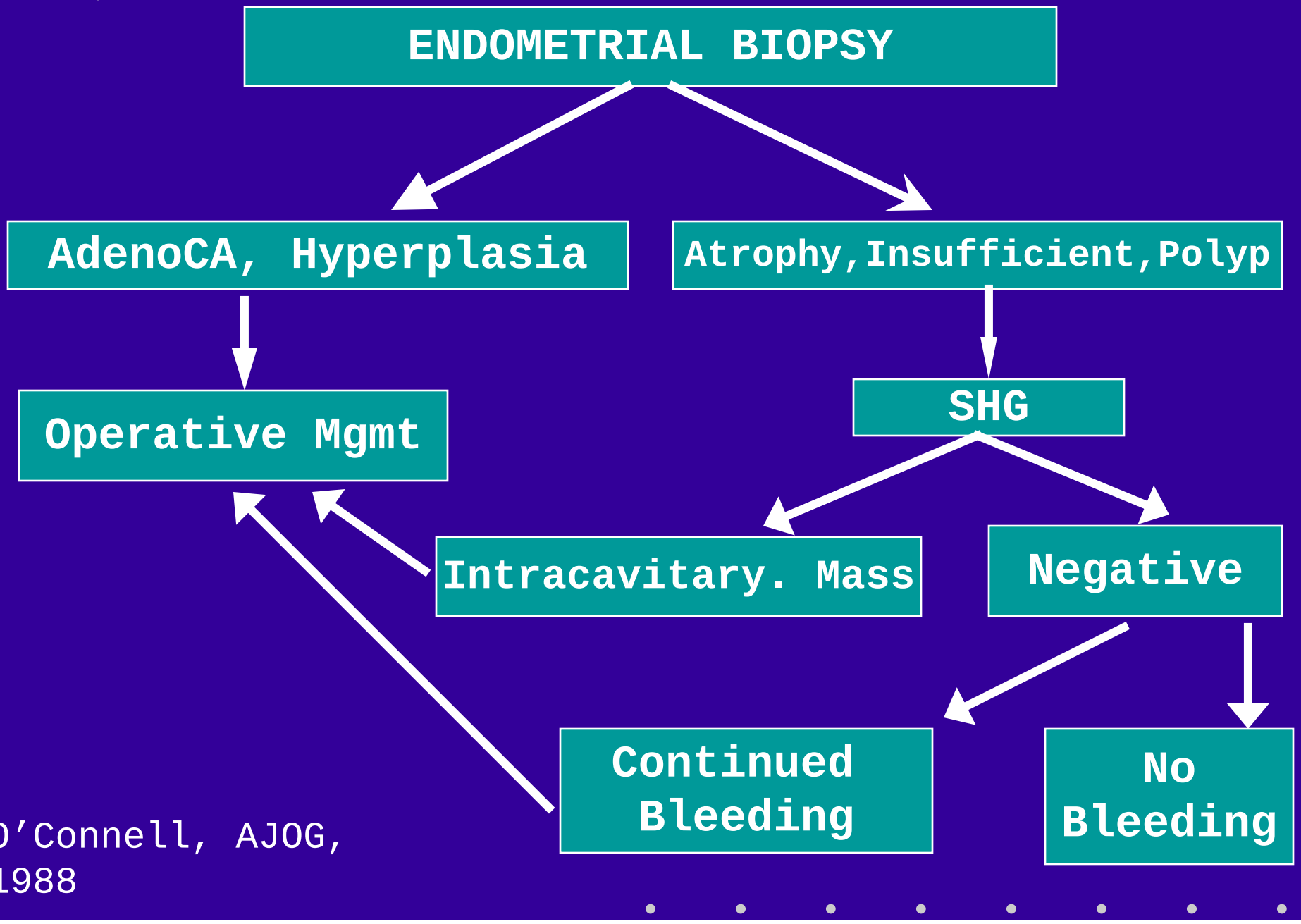
Triage of Postmenopausal Bleeding

TEST	Sensitivity	Specificity	PPV	NPV
EMB+SHG	95	98	98	96
EMB	23	100	100	60
EMS>5mm	79	57	59	74
SHG	88	96	95	90

N=92

O'Connell, AJOG, 1998

TRIAGE OF POSTMENOPAUSAL BLEEDING



O'Connell, AJOG, 1988