Cervical Cancer Screening
Vaginal Infections
Abnormal Vaginal Bleeding
Menopause and…
Osteoporosis

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No disclosures for this lecture

Pap Smear Frequency
1989 Consensus Statement

- All women who are, or who have been, sexually active, or who have reached 18 years old, should have annual Pap smears
- After at least 3 consecutive annual negative smears, Pap testing may be done less frequently
- No upper age limit on screening
- After hysterectomy, vaginal Paps every 3-5 years
- Most guidelines used risk factors to define screening intervals

Pap Smear Intervals: Made Easy

- **Start screening**
  - 3 years after first intercourse or 21 years old
  - Counsel virginal women re: benefits, risks
- **Stop screening after**
  - Total hysterectomy for a benign condition, or
  - 3 negative Paps if total hysterectomy for CIN 3, or
  - 65-70 yo, if 3 consecutive benign Paps in prior 10 yrs
- **While screening**
  - If LBC, every 1-2 years till 30, then every 2-3 years
  - If glass, yearly until 30, then every 2-3 years
  - Repeat annually if HIV+, immunocompromised, in-utero DES exposure, or history of CIN 2+

<table>
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<td><strong>Initiate Paps</strong></td>
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<td><strong>Upper age limit</strong></td>
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<td><strong>Pap interval</strong></td>
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<td>&lt; 30 yrs old</td>
<td>annual (glass) Q2 yr (LBC)</td>
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<td>≥ 30 yrs old</td>
<td>Q2-3 years</td>
<td>at least every 3 yr</td>
<td>Q2-3 years</td>
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SD: sexual debut
LBC: liquid based cytology
Post-Hysterectomy Pap Smears

- **Malignancy** (cervical cancer)
  - 3 months x 2 yrs, 6 months x 3 yrs, yearly
- **Premalignant** (HSIL)
  - Every 6 mos, until 3 benign Paps (within 10 years of hysterectomy)
- **Benign suspected, but uncertain**
  - Single cuff Pap; if benign, may discontinue
- **Benign condition**
  - Pap smears no longer necessary

Adolescents: Why Wait 3 Years to Screen?

- Very little benefit from screening in this interval
  - **Earliest HSILs appear 3 years after sexual debut**
  - Over 3 years, 97% of LSILs do not progress
  - High grade lesions are rare in adolescents
    - CIN 3 annual incidence 15-19 yo: 3/10,000
    - 4 years after HPV infection, CIN 2/3 in <5%
- **Harms**: ASC-US, LSIL findings may lead to unnecessary evaluation, treatment, and anxiety
- **In summary**
  - In the 3 years after sexual debut, the harms of screening with cervical cytology are greater than the benefits

Common Questions About Pap Intervals

- Are the intervals any different for women
  - With multiple sexual partners?
  - Using hormonal contraceptives or menopausal hormone therapy?
  - Who are pregnant?
  - Who are in a lesbian relationship?
- If a Pap is not scheduled or necessary, what about a bimanual pelvic exam?
Routine Pelvic Examination and Cervical Cytology Screening
ACOG Comm on Gyn Practice, #431. OG 2009; 113:1190

- The annual pelvic exam
  - Is a routine part of preventive care for all women 21 yo or older, even if Pap screening is not needed
  - Is not a routine part of annual assessment for women 13-21 yo, unless medically indicated
- It is reasonable to discontinue Paps at 65-70 years of age in women who have had
  - ≥3 normal cytology test results in a row, and
  - No abnormal test results in the past 10 years

Implications of 2009 ACOG Guidelines

- The good news
  - Declaration that routine pelvic exam is not necessary in an asymptomatic woman under 21 years of age
  - Permits discontinuation of Paps at 65-70 years old, if meeting specified conditions
- The bad news (…and contradicting every national CPG)
  - Still recommends an annual routine pelvic exam in women >21 years of age, even if a Pap not needed
  - “Annual (Pap) screening in women older than 30 years of age remains an acceptable option”

High Risk HPV DNA Testing
ASCCP Clinical Update 2009

Clinically useful for
- Primary screening (HPV+Pap), age 30 and over
- Triage of ASC-US or AGC Paps (≥ 21 years old)
- Triage of women who are HPV HR pos/Pap negative
  - HPV 16/18 genotyping (Cervista™ HPV 16/18)
- Post-colposcopy and post-treatment follow-up, in lieu of Pap smears

High Risk HPV DNA Testing
ASCCP Clinical Update 2009

HR HPV testing and genotyping not recommended
- Any application in women under 21 years old
- (Reflex) triage of ASC-H, LSIL, HSIL Paps
- Routine screening in women before 30 years old
- In women considering vaccination against HPV
- For routine STD screening
- Evaluation of patients with genital warts
- Evaluation of sex partners
- As part of a sexual assault evaluation
**What Are Indications for Colposcopy?**

- ASC-H, HSIL or suspicion of cancer
- LSIL in women >21 y.o. (not pregnant or menopausal)
- Atypical glandular cells (AGC)
- ASC-US result (except adolescents)
  - High-risk HPV DNA + at initial or subsequent testing
  - Repeat Pap > ASC-US during observation
  - Patient unwilling to be followed
- Cervical leukoplakia or other unexplained cervical lesion regardless of cytology result
- Unexplained or persistent cervical bleeding regardless of cytology result

**ASC-US: Women > 21 Years Old**

1. **Repeat Cytology**
   - Both Tests Negative
   - ASC
   - (in other result)

2. **Colposcopy**
   - Endometrial sampling preferred in women with abnormalities and those with unexplained leukoplakia
   - HPV DNA Testing

- HPV Positive
  - Preferred if liquid-based cytology or available
  - Manage per ASCP Guideline
- HPV Negative
  - Repeat Cytology

- Repeat Pap

**ASC-US+ LSIL: Adolescents**

- Adolescent Women with ASC-US or LSIL (females 15 years and younger)

1. **Repeat Cytology**
   - < HSIL
   - Repeat Cytology @ 6 months
   - ≥ HSIL

2. **ASC**

- Negative
  - Repeat Cytology @ 6 months
  - Colposcopy

- Routine Screening

**www.familypact.org/providers**

- **Key points, Q and A**
  - Table 1: management of non-SIL Pap smear results
  - Table 2: management of SIL, AGC Pap smear results
  - Table 3: management of biopsy results

**CLINICAL PRACTICE ALERT**

**UPDATE: MANAGEMENT OF ABNORMAL CERVICAL CYTOLGY**

Invasive cervical cancer is a preventable disease in a large majority of women, as long as preneoplastic cervical lesions are effectively detected and treated. The Family Pact Program has adopted the 2006 Consensus Guidelines of the American Society for Colposcopy and Cervical Pathology (ASCCP), which are included with this Alert.

**KEY POINTS**
- The purpose of cervical cancer screening is the detection and treatment of high-grade squamous epithelial lesions (CIN 2, 3), adenocarcinoma in situ, and cervical cancers.
**Vulvovaginitis: Differential Diagnosis**

- Vulvovaginal candidiasis (VVC)
- Vaginal trichomoniasis (VT)
- Bacterial vaginosis (BV)
- Vulvar dermatosis (LS, LSC)
- Contact dermatitis (irritant, allergic)
- Fistula: rectovaginal, enterovaginal
- Cervical origin: mucorrhea, MPC
- Physiologic, psychogenic

**Infections**

**Skin Conditions**

**Anatomic**

**Normal**

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**VT: Laboratory Tests**

Lobo, Sex Transm Dis 2003;20:694

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**VT: Treatment: CDC 2006**

- **Recommended regimen**
  - Metronidazole (MTZ) 2 grams PO single dose
  - Tinidazole (Tindamax) 2 grams PO single dose
- **Alternative regimen**
  - Metronidazole 500 mg PO BID x7days
- **Cost per dose**
  - Generic MTZ 2 gm $ 1.25
  - Flagyl 2 gm $ 15.07
  - Tindamax 2 gm $ 12.00

**BV: Pathophysiology**

- **Non-inflammatory** bacterial overgrowth
  - 100 x increase *Gardnerella vaginalis*
  - 1000 x increase in anaerobes
  - More pathogen types (*Mobiluncus, Mycoplasmas*)
- Suppression of H$_2$O$_2$-producing *Lactobacillus crispatus* and *L. jensenii* (*L. acidophilus* is not present)
- >50% women carry *G. vaginalis* in their vaginal flora in the absence of BV
  - Bacterial “C/S” of vaginal fluid doesn’t help in the diagnosis of BV….or of any other vaginal infection
**Model of BV Pathogenesis**

- Antibiotics
- Douching
- Viral phage
- Adhesion to Sperm

**Viral Depletion**
- Lactobacillus
- Anaerobes

**Increased pH**
- Suppression by amines

**WSW**
- "BVAB" (Atopobium Mobiluncus)

**BV: Sexually Associated or Transmitted?**
- "Sexually associated" in heterossexuals
  - Rare in virginal women
  - Greater risk of BV with multiple male partners
  - Condom use decreases risk,
    - But
  - No BV carrier state identified in men
  - Treatment of partner does not affect recurrences
- Women having sex with women (WSW)
  - Infected vaginal fluid between women causes BV
  - Studies of concurrence in lesbian couples suggest horizontal transmission

**BV: Clinical Presentation**
- About 50% of women with BV are asymptomatic
  - 75% no malodor, 58% no abnormal discharge
- Symptoms
  - Profuse watery discharge
  - Aminous malodor, especially after intercourse
  - Few or no irritative symptoms
- Signs
  - Homogeneous discharge: white or slate gray
  - Bubbly texture possible, but < trichomonas
  - Usually no vulvar or vaginal inflammation

**BV: Clinical Diagnosis**
- **Amsel Criteria**: 3 or more of
  - Homogenous white discharge
  - Aminous odor ("whiff" test)
  - pH > 4.5 (most sensitive)
  - Clue cells > 20% (most specific)
- **Spiegel criteria, Nugent score**: Gram stain with
  - Few or no gram positive *Lactobacillus spp.*
  - Excess of other gram negative morphotypes
## BV: Laboratory Tests

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## Who Should Be Tested for BV?

- Routine screening (asymptomatic): not indicated
- Standard diagnostic testing
  - Check discharge, amines, vaginal pH, clue cells
- Microscopy not available or inconclusive
  - Affirm VP III
  - OSOM BV Blue
  - *G vaginalis* PIP, pH+amine test cards
- “Shift in vaginal flora” on Pap
  - No consensus, but poor correlation with BV…most experts recommend no further f/u

## BV: Candidates for Treatment

- Symptomatic non-pregnant women
- Pregnant women, especially at 20-26 weeks
- Women about to have pelvic surgery
  - Induced abortion
  - Hysterectomy
  - Cervical procedure (e.g., LEEP, cone biopsy)
  - ?? IUC insertion (no evidence)
- Controversial: non-pregnant asymptomatic women with no surgery planned

## BV Treatment: CDC 2006

### Recommended regimens
- Metronidazole 500 mg PO BID x 7 days
- Metronidazole gel 0.75% 5g per vagina QD x 5 days
- Clindamycin 2% cream 5g per vagina QHS x 7 days
- Clindamycin SR 2% cream* as single dose

### Alternative regimens
- Metronidazole 2 g PO x 1
- Clindamycin 300 mg PO BID x 7 days
- Clindamycin ovules 100 mg per vagina QHS x 3 days

* Not listed in CDC guidelines, but cure rate equivalent to Cleocin vag
**Recurrent Bacterial Vaginosis**

- Consider suppression with MTZ vaginal gel twice weekly (after initial treatment)
- Abstain from vaginal sex during treatment
- Don’t douche…with anything!
- Use of condoms (esp in 1st month after treatment) may reduce recurrences
- Clean sex toys (or use condoms) between use by one woman then another
- Avoid vaginal insertion following anal insertion of fingers or penises

**VVC: Laboratory**

- **NaCl suspension**: many WBC, normal LB
- **KOH suspension**
  - C. albicans: pseudohyphae and blastospores (buds)
  - C. glabrata: blastospores only
- **Gram stain**: gram pos hyphae and buds
- **pH**: 4-6
- **Amine test**: negative
- **Culture**: Nickerson's, Sabauraud's
- **Candida PCR (lab); Affirm VP III (point of care test)**

**VVC Classification: CDC 2006**

- **Uncomplicated VVC (80-90%)**
  - Sporadic or infrequent VVC, and
  - Mild-to-moderate VVC, and
  - Likely to be Candida albicans, and
  - Immune competent
- **Complicated VVC (10-20%)**
  - Recurrent VVC, or
  - Severe VVC, or
  - Non-albicans candidiasis, or
  - Uncontrolled DM, immunosuppression, pregnancy

**Uncomplicated VVC: Treatments**

- **Non-pregnant**
  - 3 and 7 day topicals equal efficacy and price
  - Use: 1 or 3 day topical or fluconazole PO
- **If first treatment course fails**
  - Re-confirm diagnosis (r/o dual infection)
  - Treat with an alternate antifungal drug
  - Perform Candidal **culture** to confirm and speciate
- **No role for nystatin, candididin**
**Complicated VVC: CDC 2006**

**Severe VVC**
- Advanced findings: erythema, excoriation, fissures
- Topical azole therapy for 7-14 days, or

**Compromised host**
- Topical azole treatment for 7-14 days
- Fluconazole 150 mg PO; repeat Q3 days 1-2 times

**Pregnancy**
- Topical azoles for 7 days

**Recurrent VVC (RVVC)**
- ≥ 4 episodes of symptomatic VVC per year
- Most women have no predisposing condition
  - Partners are rarely source of infection
- Confirm with *Candida* culture before maintenance therapy; also check for non-albicans species
- Early treatment regimen: self-medication 3 days with onset of symptoms

**Complicated VVC: CDC 2006**

**Recurrence VVC**
- Treat for 7-14 days of topical therapy or fluconazole 150 mg PO q 72° x3 doses, then
- Maintenance therapy x 6 months
  - Fluconazole 100-200 mg PO 1-2 per week
  - Itraconazole 100 mg/wk or 400 mg/month
  - Clotrimazole 500 mg suppos 1 per week
  - Boric acid 600 mg suppos QD x14, then BIW
  - Gentian violet: Q week x2, Q month X 3-6 mo

**AVB: Differential Diagnosis**

- Early pregnancy
- Ovulatory bleeding
  - Structural Conditions
  - Non-Structural Conditions
- Iatrogenic (medications)
- Anovulatory bleeding
  - Estrogenic or Hypoestrogenic
  - Aka: *Dysfunctional Uterine Bleeding*
Abnormal Vaginal Bleeding

- Hx, PE, Preg test
- Preg test POS → Pregnant
  - Location
  - Viability
  - GA Dating
- Preg test NEG → Ovulatory
  - Location
  - Viability
  - GA Dating
  - Estrogenic
    - Menarche
  - Iatrogenic
    - Menopause
  - Hypo-E
    - Hyperplasia
    - EM Cancer

- (Oligo) Anovulation
  - Structural
    - Myoma
    - Polyp
    - Foreign body
    - Cx cancer
    - Idiopathic
  - Non-Structural
    - PID
    - Cervicitis
    - Atrophic vag
    - Coagulopathy
    - LPD
  - Estrogenic
    - Menarche
    - Menopause
    - PCOS
    - Hyperplasia
  - Hypothalamic dysfunction
    - Pituitary dysfunction
    - Ovarian dysfunction

- Dysfunctional Uterine Bleeding
  - What causes anovulatory bleeding?
    - Excess androgen: PCOS; acute stress
    - Excess estrogen: unopposed exogenous or endogenous estrogen
    - Excess prolactin: prolactinoma, drugs, lactation
    - Age-related: peri-menarche, perimenopause

- PCOS: Overlapping Syndromes
  - Insulin Resistance
  - Hyper-Androgenism
  - Chronic Anovulation
  - PCOS

- AVB: History
  - Is the patient pregnant?
    - Pregnancy sxs, esp. breast tenderness
    - Intercourse pattern, contraceptive use
  - Is bleeding ovulatory or anovulatory?
    - Bleeding pattern: regular, irregular, none
    - Molimenal sxs: only in ovulatory cycles
    - Previous history of menstrual disorders
    - Recent onset weight gain or hirsuitism
    - Hx bleeding dyscrasia or endocrinopathy

- * Hyperandrogenism (clinical or biochemical)
- * Chronic oligo-ovulation
- * Exclusion of other disorders
[PCO on ultrasound in Rotterdam criteria set]
AVB: Physical Exam
- General: BMI ≥ 30, acne, hirsutism
- Breasts: galactorrhea
- Abdomen: uterine enlargement, abdominal pain
- Pelvic: uterine enlargement or softness, masses
- Cervical mucus

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AVB: Laboratory
- Urine highly sensitive pregnancy test
  - Quantitative B-hCG is not necessary
- CBC (or hemogram)
  - Detect severe anemia; baseline value for observation
  - Platelet estimation (detect thrombocytopenia)
- “Coagulation panel”
  - Only in teens recurrent menorrhagia (vWD) or other reason to suspect coagulopathy (liver disease, ITP)
- TSH, PRL if recurrent anovulatory bleeds
- FSH, LH, estradiol levels are not helpful

Evaluation of PCOS
- PCOS is a clinical diagnosis
  - Oligo-anovulation (or DUB) + hyperandrogenism
  - Lab tests may be necessary to...
    - Differentiate PCOS from other causes of
      » Virilization
      » Amenorrhea
    - Screen (or test) for sequelae of PCOS
      » Metabolic syndrome (DM, lipids, HTN)
      » Endometrial hyperplasia
  - Choose optimal drug for ovulation induction

Basic Evaluation of PCOS
- Check blood pressure
- Measure BMI + waist circumference (+ hip)
  - Waist circumference >35 inches
  - Waist/hip ratio > 0.72
- In women with “clinical PCOS”, screen for
  - T2DM: 2º PGL test with 75-g glucose load
  - Hyperlipidemia: fasting lipid panel
  - Screen both every 2 years
**Further Evaluation of PCOS**

- If dysfunctional uterine bleeding, **add**
  - Pregnancy test, hematocrit
  - Endometrial biopsy if hyperplasia suspected
- If hirsuitism, **add**
  - 17a-hydroxy progesterone (17-OHP)
  - Total testosterone (optional at this step)

**Further Evaluation of PCOS**

- If virilization (in addition hirsuitism), **add**
  - DHEAS (for adrenal tumor) and
  - Free or total testosterone (for ovarian tumor)
  - If ↑T, pelvic ultrasound for ovarian tumor
- If stigmata of Cushing’s Disease, **add**
  - Urinary 24 hour free cortisol or
  - Overnight dexamethasone suppression test

**Management of Episodic DUB**

- Substitute a pharmacologic luteal phase for missed physiologic luteal phase
- If minimal bleeding for a few days
  - Rx MPA 10 mg QD (or microP, 200 BID) x10d
  - Bleeding stops < 3 days; w/d after progestin
- Moderate or heavy bleeding > 3 days
  - Monophasic OC given BID- TID x 5-7 days
  - OC “taper” (QID-TID- BID-QD) and then stopping is illogical and should not be used
- Torrential bleed: surgical curettage (MUA)

**Management of Recurrent DUB**

- **Pregnancy**: clomiphene or metformin
- **Contraception**: cycle with OC
- Not interested in pregnancy or contraception
  - MPA or microP first 10-14 days each month
  - Withdraw every other month to document ovulation
- Peri-menopausal bleeding
  - Once hyperplasia excluded, goal=cycle control
  - Low estrogen dose OC
  - Cyclic sequential HT
**Postmenopausal Bleeding: Differential Diagnosis**

- Exogenous estrogens
  - HT (therapy formerly known as HRT)
- Endogenous estrogens
  - Acute stress
  - Estrogen-secreting ovarian tumor
- Atrophic vaginitis
- Endometrial hyperplasia/adenocarcinoma
- Endometrial hypoplasia (atrophy)

**Postmenopausal Bleeding: Management**

- If not using HT, endometrial evaluation is required
  - Endometrial biopsy (EMB)
  - Endovaginal ultrasound (normal stripe is < 5 mm)
- If using HT, EMB to evaluate unscheduled bleeding or bleeding > 3 months after initiation
- Therapy is tailored to the site of bleeding
  - Atrophic vaginitis: topical estrogen
  - Endometrial hyperplasia: continuous P x 3-6 months, then re-biopsy
  - Endometrial atrophy: cyclic or continuous HT

**Who Needs an EMB?**

- **Purpose:** detect endometrial hyperplasia or cancer
- **Menopausal woman**
  - Any postmenopausal bleeding, if not using HT
  - Unscheduled bleeding on continuous-sequential hormone therapy
  - Bleeding > 3 mo after start of continuous-combined hormone therapy
  - Endometrial stripe ≥ 5 mm (applies to postmenopausal woman only)
  - Pap smear: any endometrial cells or AGC Pap

**Who Needs an EMB?**

- **Premenopausal Women**
  - Prolonged *metrorrhagia*
  - Unexplained post-coital or intermenstrual bleeding
  - Endometrial cells on Pap smear in anovulatory premenopausal woman
  - Atypical glandular cells (AGC) Pap
    - Abnormal endometrial cells
    - Older than 35 years old
    - < 35 yo with abnormal bleeding

Available at: menopause.org

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Diagnosis of Menopause

- **Surgical menopause** can be assumed after bilateral oophorectomy
- **Natural menopause**
  - Average age: 51.4 years old; range: 40-55 y.o.
  - Diagnosis
    » Amenorrhea (12 mo)+ symptoms if > 45 yo (OR)
    » FSH >30 mIU/mL and E₂ < 30 pg/mL
    » However, single random levels of FSH or E₂ may not be reliable indicators of menopause...if in doubt, repeat

Post-WHI Thinking

- The CVD findings of WHI and HERS apply mainly to women 60 years of age and older
- Recent re-analyses show mild cardioprotective effect for HT users in their early 50s
  - But, there is no indication to prescribe HT for the purpose of cardioprotection at any age
- When used to treat menopausal symptoms, the benefits of HT exceed the known risks of HT
  - Shortest period of exposure
  - Lowest effective dose
**HT & Breast Cancer**

- Breast cancer risk ↑ with EPT use >3-5 years
- Increased absolute risk of EPT in WHI: “rare”
  - 4-6 additional cases/10,000/yr of EPT for ≥ 5 yrs
- Unclear whether EPT risk differs between continuous and sequential progestogen use
- Estrogen only regimens
  - WHI ET trial showed no increased risk after 7.1 yrs
  - 6 fewer cases/10,000 women/yr of ET use
  - ET for < 5 yrs has little impact on breast cancer risk

NAMS position statement. *Menopause* 2008. (cont’d)

**HT & Breast Cancer (cont’d)**

- EPT and, to a lesser extent, ET, increase breast cell proliferation, breast pain, and mammographic density
- EPT may impede diagnostic interpretation of mammograms
- Whether to use HT when history of breast cancer is unresolved (limited epidemiologic evidence mixed; no completed long-term RCTs)


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**Hot Flashes: Lifestyle Changes**

- Exercise routinely, at least 3-4 days/week
- Cool room temperature, especially at night
- Dress in layers (remove outer layers if warm)
- Avoid hot and spicy foods
- Relaxing activities
- Avoid cigarettes
- Minimize alcohol

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**Botanicals and PhytoSERMs**

*Probably better than placebo*

- Black cohosh
  - No evidence of efficacy
- Soy isoflavones
- Red clover isoflavones
- Evening primrose oil
- Dong quai
- Ginseng
- Vitamin E
- Chasteberry (Vitex)

Not better than pbo
Not better than pbo
Not better than pbo
Not better than pbo
Not better (as monotx)
Not better than pbo
Not better than pbo
No studies
Non-hormonal Hot Flash Therapies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Hot Flash Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antidepressants</strong></td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>62-65%</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>38-60%</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>20%</td>
</tr>
<tr>
<td><strong>Anticonvulsants</strong></td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>45%</td>
</tr>
<tr>
<td><strong>Antihypertensives</strong></td>
<td></td>
</tr>
<tr>
<td>Metyldopa</td>
<td>65%</td>
</tr>
<tr>
<td>Clonidine</td>
<td>38%</td>
</tr>
</tbody>
</table>

Menopause 2004; 11(1): 11-33

ACOG Task Force on HT Obstet Gynecol 2004; 104:106s-17s.

Prescription HT Options: ET and EPT

<table>
<thead>
<tr>
<th></th>
<th>Oral</th>
<th>Transdermal</th>
<th>Intravaginal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ET</strong></td>
<td>• Micronized estradiol</td>
<td>• Patches</td>
<td>• Creams</td>
</tr>
<tr>
<td></td>
<td>• Conjugated equine estrogens (CEE)</td>
<td>• Gels</td>
<td>• Intravaginal tablet</td>
</tr>
<tr>
<td></td>
<td>• Synthetic conjugated estrogens</td>
<td>• Emulsion</td>
<td>• Rings</td>
</tr>
<tr>
<td></td>
<td>• Esterified estrogens</td>
<td>• Spray</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Estropipate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Estradiol acetate</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EPT</strong></td>
<td>• CC-EPT</td>
<td>• E+P (combination) patches</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• CS-EPT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


HT Regimens

<table>
<thead>
<tr>
<th>Month 1</th>
<th>Month 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen Therapy (ET)</td>
<td>Estrogen</td>
</tr>
<tr>
<td>Continuous combined (CC) EPT</td>
<td>Progestin</td>
</tr>
<tr>
<td>Continuous-sequential (CS) EPT</td>
<td>Progestin 14d</td>
</tr>
<tr>
<td>Estrogen 14d</td>
<td>Off for 14 d</td>
</tr>
<tr>
<td>Continuous-pulsed (CP) EPT</td>
<td>3d</td>
</tr>
</tbody>
</table>

Choice of HT Regimen

- If no uterus: estrogen only
- If uterus present
  - Goal is to avoid vaginal bleeding entirely, or, at least, to make it predictable
  - Endometrial activity predicts bleeding pattern
    - Recent spontaneous or induced bleeding
      » Continuous sequential
    - No bleeding for >2-3 cycles
      » Continuous combined
**HT Starting Dosages**

- Lower daily doses typically used with systemic ET
  - 0.3 mg oral CE
  - 0.5 mg oral micronized 17β-estradiol
  - 0.014-0.025 mg transdermal 17β-estradiol patch
- Typical lowest doses of progestogen
  - 1.5 mg oral MPA
  - 0.1 mg oral norethindrone acetate
  - 0.5 mg oral drospirenone
  - 50-100 mg oral micronized progesterone


**Compounded Hormone Therapy**

Compounded hormones will probably work about as well as commercial HT products, but...

- The value of adding E_1 + E_3 has not been evaluated
- Progesterone skin cream is not absorbed
- Compounded hormone doses are not standardized
- Salivary hormone levels are not useful
- FDA-approved HT products will offer
  - Bioidentical hormones
  - Choice of delivery systems
  - Formulary coverage/ lower out-of-pocket costs

**Treatment of Hot Flashes**

- If mild sxs, try exercise, black cohosh + phytoSERM
- Initiate low dose HT if
  - Moderate or severe symptoms
  - Non-hormonal treatments have failed
  - No interest in non-hormonal therapy
- Titrate estrogen dosage upward if needed
- When estrogen can’t be used, offer
  - SSRI or SNRI
  - Gabapentin, clonidine, a-methyldopa,
  - MPA or Megesterol (Megace)
- Attempt discontinuation after 1-2 years

**Treatment of Sleep/ Irritability Sxs**

- If mild symptoms
  - Lifestyle change, black cohosh, phytoSERMs
- If severe symptoms or no response to above
  - Low dose HT, then titrate upward
  - If mood swings, transdermal E preferred
- Depression component, or no response to HT
  - SNRI or SSRI
**HT and Vaginal Atrophy**

- When HT is considered solely for this indication, local (not systemic) vaginal ET is generally recommended.
- Progestogen generally *not indicated* with low-dose, local vaginal ET.
- Vaginal lubricants often improve vaginal dryness and painful intercourse.


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**Vaginal Estrogen Therapies**

<table>
<thead>
<tr>
<th>Product</th>
<th>Brand</th>
<th>Dosage</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjugated estrogen cream</td>
<td>Premarin cream</td>
<td>0.625 mg/ gram</td>
<td>Daily, then 1-3 time/wk</td>
</tr>
<tr>
<td>Estradiol cream</td>
<td>Estrace</td>
<td>0.01% (0.1 mg/ gm)</td>
<td>Daily, then 1-3 time/wk</td>
</tr>
<tr>
<td>Estradiol vaginal tablet</td>
<td>Vagifem</td>
<td>25 micrograms</td>
<td>Daily for 2 wks, BIW</td>
</tr>
<tr>
<td>Estradiol ring</td>
<td>Estring</td>
<td>7.5 mcg/ 24 hrs</td>
<td>Every 90 days</td>
</tr>
<tr>
<td>Estradiol ring*</td>
<td>Femring</td>
<td>0.05 mg/d 0.1 mg/d</td>
<td>Every 3 months</td>
</tr>
</tbody>
</table>

*Intended to be used as systemic HT*

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**HT & Urinary Health**

- Local ET may benefit some women with urge incontinence who have vaginal atrophy.
- Unclear if ET by any route is effective for overactive bladder.
- Controversial if local ET can improve stress incontinence (systemic ET may worsen or provoke it).
- Local vaginal ET may reduce risk of recurrent UTI.
- No HT product approved for urinary health in US/Canada.


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**HT & Cognitive Aging/Decline, Dementia**

- HT not recommended at any age for the sole or primary indication of preventing cognitive aging or dementia.
- HT seems to increase dementia incidence when initiated at ≥65 years old.
- Inadequate data if HT started soon after menopause increases or decreases later dementia risk.
- Limited data do not support HT for Alzheimer’s disease.

**HT and Cognition**

- Many women experience worsening of short term memory with onset of menopause
- 9 RCTs and 8 cohort studies
  - HT does not improve cognitive performance in women without symptoms
  - If symptoms, HT improved verbal memory, reasoning, and motor speed tests
- Reasonable to provide HT to lessen cognitive changes in symptomatic menopausal women

**HT and “Quality of Life”**

- RCTs and retrospective studies show that HT has no effect on “quality of life” measures
- Many woman who wean from HT state that they “feel worse”…even after 20 years after menopause!
- Conventional wisdom
  - In women who “feel better on/ worse off” of HT, continue low dose HT if few or no risk factors
  - When (& how often) to re-attempt wean uncertain
  - Don’t start HT for solely for improving QOL

**HT Duration of Use**

- No clear indication that longer HT duration improves or worsens the benefit-risk ratio
- Long-term risks not yet studied in perimenopausal women
- Thus, findings from RCTs of postmenopausal women should be extrapolated with caution for younger women
- Extending HT use is acceptable
  - For women well aware of potential risks and benefits
  - With lowest effective dose
  - For prevention of further osteoporosis-related fracture when alternate therapies not appropriate
  - With clinical supervision


**Discontinuation of HT**

- After 2 years, recommend a trial of HT discontinuation
- Is tapering from hormone therapy necessary?
  - Grady D, Obstet Gynecol 2003;102:1233
  - n=377 who attempted discontinuation of HT
  - 74% successfully stopped; 26% resumed
  - 71% stopped abruptly; 29% tapered: equal success
- “Rebound” hot flashes occur in some women and can last up to 3 months…many experts recommend a taper
  - Taper hormone therapy over 8-12 weeks
  - Reduce dose or extend intervals (every 2, then 3 days)
  - Cut patches in half
Predictors of Osteoporotic Fracture

- Low impact fracture (2-8x)
- Age > 60 years old (2-3x each decade >50)
- Bone-related risk factors (1.2-2.0 x)
  - Race/ethnicity: white > Hispanic, Asian > black
  - Slender, sedentary, poor calcium intake, family history, smoker, drinker, height loss >2 cm
- Low bone mineral density
  - 1.5-1.8x for each SD decrease T-score
- Fall risk factors: poor vision, ↓ hand grip strength

Candidates for “Routine” BMD Screening

Does treatment of low BMD prevent fractures?

USPSTF 2002
- No risk factors
- Risk Factors

NOF 1998
- No risk factors
- Treat, no BMD

BMD Screening: NOF 2008

- Women 65 years old and older
- Adults who have had a fracture after age 50
- Perimenopausal women with a specific fracture risk: low body weight, prior low impact fracture, high risk medication
- Adults with a condition, or taking a medication, associated with low bone mass or bone loss
- Anyone being treated for osteoporosis, to monitor treatment effect

BMD Screening: NOF 2008

- Younger postmenopausal women about whom you have concern based on clinical risk factor profile
- Postmenopausal women discontinuing estrogen “should be considered” for BMD testing
- Anyone being considered for pharmacologic treatment
- Anyone not receiving therapy in whom evidence of bone loss would lead to treatment....huh???

WHO Fracture Risk Assessment

- Current age
- Gender
- Femoral neck BMD
- Body mass index
- Current smoking
- Alcohol intake ≥ 3 drinks per day

- Use of glucocorticoids
- Secondary osteoporosis
- Personal history of fracture
- Parental history of hip fracture

National Osteoporosis Foundation
February 2008

- Exercise: aerobic + strength training
  - Improve bone density, improve balance
  - Reduction in hot flashes in some women

- Calcium, Vitamin D
  - Adults under age 50 need, per day
    » 1,000 mg of calcium*
    » 400-800 IU of vitamin D₃
  - Adults 50 and over need, per day
    » 1,200 mg of calcium*
    » 800-1,000 IU of vitamin D₃
  * In divided doses, preferably with meals

Osteoporosis Treatments

<table>
<thead>
<tr>
<th>Name</th>
<th>Delivery</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcitonin</td>
<td>Intranasal, daily</td>
<td>Reduces bone pain</td>
<td>Less effective for fracture prevention</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>Tablet, daily</td>
<td>Protects breast</td>
<td>Daily use, less effective</td>
</tr>
<tr>
<td>Alendronate</td>
<td>Tablet or solution, weekly</td>
<td>Reduces hip and spine fractures</td>
<td>GI side effects</td>
</tr>
<tr>
<td>Risedronate</td>
<td>Tablet, weekly</td>
<td>Reduces hip and spine fractures</td>
<td>•GI side effects •Less hip protection than alendronate?</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>PO, monthly IV, Q3 months</td>
<td>Convenience</td>
<td>No protection for non-vertebral fractures</td>
</tr>
<tr>
<td>Zolendronate</td>
<td>IV, annually</td>
<td>Convenience</td>
<td>Cost</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>Injection, daily</td>
<td>Used for severe cases</td>
<td>Cost, daily injection osteosarcoma risk</td>
</tr>
</tbody>
</table>

Follow-up of Treated Patients

- Primary outcome
  - Was fracture prevented?

- Short term (4 mo) surrogate marker: if BTOM (NTx) is reduced, Rx is being used and is working

- Long term: repeat DEXA every 2 years
  - >90% women will gain BMD with treatment; about 10% are non-responders
  - Monitoring may reinforce adherence
  - Therefore,
    » If BMD is stable (or higher), Rx is working
    » If BMD continues to fall, change strategy
2º Prevention of OP Fractures: Is there a Role for “OP Prophylaxis”

- Makes sense that preserving bone mass will prevent bone fractures…but little evidence to prove it
- Women over 60 years old
  - T score less than -1.6: tx prevents fractures
  - T score higher than -1.6: no fracture prevention
- Women under 60 years old
  - Treatment increases BMD
  - No data that treatment reduces fractures
  - No data that treatment reduces fractures when older than 60 as a result of treatment in 50s

Hormone Therapy and Fracture Prevention

Pros
- Good data on fracture prevention (mainly 2º prevention)
- Relatively lower cost than bisphosphonates
- Less concern of adverse effects with ET alone (vs EPT)

Cons
- Requires long term use and surveillance
- Post-menopausal bleeding can be troublesome
- Increased risk of breast cancer after 5 years of use

Utility
- Fracture prophylaxis if using HT for another indication
- Otherwise, consider bisphosphonates as first line

OP: Take-Home Messages

- All women should engage in behaviors that preserve bone mineral density
  - Exercise, calcium supplements, limit alcohol, don’t smoke
- High risk women should be treated routinely
  - Personal history of low impact fracture as adult
  - > 70 years old with multiple fracture risk factors
- Other treatment decisions should be based on
  - Age > number of fracture risk factors > BMD (T score)
- The value of osteoporosis prophylaxis provided to women in their 50s to prevent fractures in their 60s is uncertain and has not been proven by evidence