Perimenopause, Paps, Polyps and Beyond

Gynecology Pearls for the Internist

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Where are we going in the next 45 minutes?

• Perimenopause (Pearls on management of menopausal symptoms)
• Paps (Making sense of the new cervical cancer screening guidelines)
• Polyps (Abnormal uterine bleeding, Tricks of the Trade)
The definition of Hot Flash:
Your body deciding to spontaneously combust while taking you on a secret rollercoaster ride through the bowels of Hell.

Hot Facts

• Perimenopause = Menopausal Transition
  – Marked by fluctuations in hormone levels as ovarian function slows
  – Estrogen/Progesterone decrease, FSH increases

• Menopause
  – Occurs one year after LMP/ loss of ovarian activity
  – North American women – median age 51 yo
  – 1/3 of our lives spent beyond menopause....
Vasomotor Symptoms i.e. Global Warming

- Experienced by 80% of women, 33% > 10/day
- Last 1-5 minutes
- Range of symptom duration: 4 – 10.2 years
- Symptoms
  - Sensation of extreme heat
  - Perspiration, flushing, anxiety, chills
  - Heart palpitations
  - Sleep disturbances

Pathophysiology (of hot flushes, not global warming)

- Change of Thermoregulatory Mechanisms
  - More sensitive to subtle changes in core body temperature
  - Small increase in temperature triggers mechanism that causes hot flush
  - Hormonally mediated, but not the sole cause
**Risk Factors Based on Epidemiologic Studies**

- Study of Women’s Health Across the Nation
  - 15,000 women age 40-55
  - African Americans reported most vasomotor sx
  - Asian American women, the fewest
  - Contribution of diet (soy based) vs cultural perceptions and expectations
  - More common in obese women
    - Hypothesis is that adipose tissue acts as an insulator

**Guiding Principles for Treatment of Menopausal Symptoms**

- Systemic Hormone Therapy with Estrogen alone or in Combination with Progesterone is the Most Effective therapy for vasomotor symptoms
- Low Dose systemic doses of Estrogen are associated with better adverse effect profile than standard doses and reduce vasomotor symptoms
**Guiding Principles**

- The risks of combined hormone therapy (HT) include thromboembolic disease and breast cancer
- Given variable response and associated risk of HT, care should be individualized with the lowest effective dose for the shortest duration
- SSRIs, SSNRIs, Clonidine and Gabapentin can be effective alternatives. Paroxetine is the only FDA approved non hormonal tx for vasomotor symptoms

**The Swinging Hormonal Pendulum**

- Women’s Health Initiative 2001
- Large RCT, 27,000 women 55-77 yo
- Goal was to assess HT for prevention of CHD
- Trial was stopped after an increase in Breast cancer (8/10,000), Thromboembolic events and stroke (8/10,000) and Coronary Heart Disease (7/10,000) was seen after 5 years of combined HT (Premarin and Provera)
Weaknesses and Re-analysis of WHI

• Average age of participant = 63 years old
• 45% were obese, 10% were smokers, 36-48% had hypertension
• Increase in breast cancer Not seen in users of Estrogen alone (also decreased morbidity)
• Cannot generalize results to younger women

Systemic Hormonal Treatment

• Individualize care and treat with the lowest effective dose for the shortest duration needed to relieve symptoms
• Low Dose Estrogen
  – CEE (Premarin) 0.3-0.45mg/day
  – Micronized Estradiol (Estrace) 0.5 mg/day
  – Transdermal Estradiol Patch (Climara, Vivelle) 0.025mg/day
  – Transdermal Estradiol Gel 0.06%, 0.74 mg/day
Transdermal estrogen products

Active Ingredient(s) | Product Name(s) | Dosage (mg E2/day)
---|---|---
Patch
17β-estradiol* | Alora† | 0.025, 0.05, 0.075, 0.1 l/week
Climara | 0.025, 0.05, 0.075, 0.1, 0.075, 0.1 l/week
Estromin² | 0.05, 0.1 l/week
Estroval² | 0.025, 0.075, 0.1 l/week
Mireval² | 0.25, 0.075, 0.075, 0.1 l/week
Oesclim² | 0.025, 0.075, 0.1 l/week
Vivelle-Dot† | 0.025, 0.075, 0.1 l/week
Various generics
Transdermal gel
17β-estradiol* | Divigel | 0.25, 0.5, 1.0
EstroGel | 0.25, 0.5, 1.0 (usually cyclic, adjust to control symptoms)
Elestrin† | 0.52 (adjust based on individual response)
Transdermal spray
17β-estradiol* | Evamist† | 1.53 (1 spray/d initially, adjust dosage by response)

*Bioidentical defined as compounds that have the same chemical and molecular structure as hormones that are produced in the body.
†Available in the United States but not Canada
‡Available in Canada but not the United States

Approved Prescription Products for Menopausal Symptoms in the United States and Canada

Oral estrogen products

Active Ingredient(s) | Product Name(s) | Dosages (mg/d)
---|---|---
17β-estradiol* | Estrace‡ | 0.5, 1.0, 2.0 (administer cyclically)
Various generics
Conjugated estrogens | Premarin | 0.3, 0.45, 0.625, 0.9, 1.25
Synthetic conjugated estrogens, B | Enjuvia† | 0.3, 0.45, 0.625, 0.9, 1.25
Conjugated estrogens, CSD (synthetic) | "C.E.S."* | 0.3, 0.625, 0.9, 1.25
"Prem-Compound estrogens, CSD"* | 0.3, 0.625, 0.9, 1.25
Estradiol | Mestranol* | 0.3, 0.625, 1.25, 2.5 (administer cyclically)
Estrogyn* | 0.3, 0.625 (administer cyclically)
Estrapipate | Various generics| 0.025 (0.75 estrogens), 1.25 (1.5), 2.5 (3.0), 5.0 (6.0)

*Bioidentical defined as compounds that have the same chemical and molecular structure as hormones that are produced in the body.
†Available in the United States but not Canada
‡Available in Canada but not the United States

Product names not marked are available in both the United States and Canada.
PEARL ALERT!

• Tips when considering Hormone Therapy
  – Transdermal Estrogen has a lower risk of VTE compared to Oral (d/t prothrombic effect of oral)
  – Transdermal patches, gel, and ring bypass GI conversion of Estradiol to Estrone resulting in less impact on Triglycerides
  – Synthetic Progestins (Provera, Norethindrone) are associated with increased VTE risk while Natural Progestin (Prometrium) is not.

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<th>Active Ingredient(s)</th>
<th>Product Name</th>
<th>Dosage</th>
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| Oral continuous-cyclic
Conjugated estrogens (E) + medroxyprogesterone acetate (P) | Premphase* | 0.625 mg E + 5.0 mg P (2 tablets: E days 1-14, E + P days 15-28)
| | Premplus Cycle† | 0.625 mg E + 10.0 mg P (2 tablets: E days 1-14, E + P days 15-28) |
| Oral continuous-combined
Conjugated estrogens (E) + medroxyprogesterone acetate (P) | Prempro* | 0.3 or 0.45 mg E + 1.0 mg P* 
| | | 0.625 mg E + 2.5 or 5.0 mg P |
| Estriol estradiol (E) + norethindrone acetate (P) | Extiron*, FerriHRT Lo† Extiron*, FerriHRTVT† | 2.5 µg E + 0.5 mg P |
| | | 5 µg E + 1 mg P |
| 17β-estradiol (E) + norethindrone acetate (P) | Activelle*, Activelle LD† | 0.5 mg E + 0.1 mg P, 1 mg E + 0.5 mg P |
| | | 1 mg E + 0.5 mg P |
| 17β-estradiol (E) + drospirenone (P) | Angeliq | 1 mg E + 0.33 mg P, 0.6 mg E + 0.5 mg P |
| Oral intermittent-combined
17β-estradiol (E) norgestimate (P) | Prefest* | 1 mg E and 1 mg E + 0.09 mg P (E alone for 3 d, followed by E+P for 3 d, repeated continuously) |
| | | 1 mg E and 1 mg E + 0.2 mg P |
| Conjugated estrogens (E) + medroxyprogesterone acetate (P) | Premplus Cycle† | 0.625 mg E + 10.0 mg P (2 tablets: E for 28 d, P days 15-28) |
| | | 0.625 mg E + 15.0 mg P |
| Transdermal continuous-combined
17β-estradiol (E) + norethindrone acetate (P) | CombiPatch* Estalis† | 0.05 mg E + 0.14 mg P transderm. 0.05 mg E + 0.25 mg P transderm |
| | | 0.066 mg E + 0.015 mg P |

*Available in the United States but not Canada
Available in Canada but not the United States
Products not marked are available in both the United States and Canada
Bioidentical Hormones (just say no to buccal swabs...)

- “Plant derived hormones chemically similar or structurally identical to those produced in the body”
- FDA Approved: Estradiol, Micronized Progesterone
- Non FDA Approved: BIEST, TRIEST, DHEA, compounded blending of commercial agents

Compounded Bioidentical Hormones

- No rigorous clinical testing for efficacy, safety, potency
- Risk of under or overdosing
  - Lack of endometrial protection, risk of hyperplasia
- No evidence that salivary testing of hormones is biologically meaningful
  - Inconsistent levels of circulating hormones, large variability with individual patients, time of day, diet
Non Hormonal Medications for treatment of Vasomotor symptoms

- SSNRI Venlafaxine 100 mg/day. 62% study participants had reduction of 5.35 hot flushes/day
- Meta analysis SSRIs and SSNRIs – significant reduction vs placebo
- Paroxetine 7.5 mg/day only FDA approved
- Clonidine 0.1 mg/day and Gabapentin (600-900mg/day) small benefit, not FDA

Angelina Jolie-Pitt
BRCA Preivor

- Young BRCA Carriers electing for risk reducing mastectomies and BSO
- Evidence shows surgically menopausal women <40 yo, increased risk dementia, Parkinson’s
- Studies show short term use of systemic HT does not increase cancer risk in those with intact breasts
- Angelina: Transdermal Estradiol + off label use of Levonorgestrel IUD for endometrial protection
The Sahara Desert-Vaginal Dryness

- Low dose systemic estrogens alleviate symptoms
- Local administration with Cream, Ring, Tablet
- Start with daily treatment for 1-2 weeks, then once weekly for maintenance
- Estring (3 months) preferred over cream
- Systemic absorption documented, but at normal doses, no progesterone needed

Up and Coming for Hot and Dry

- Ospemifene (Osphena) for vaginal atrophy
  - No endometrial stimulation, 60 mg/day
  - Side effect- hot flushes
- Femring- Systemic HT delivered vaginally
  - 0.05mg/day or 0.10mg/day. Treats vasomotor sx and vaginal atrophy for 3 months
- Duavee – SERM + Estrogen
  - Premarin 0.625 mg and Bazedoxifene 20 mg
Final Pearls: Hormone Therapy

- Insufficient evidence to support tapered vs abrupt discontinuance of HT
- HT should not be used for primary or secondary disease prevention
- The use of menopausal HT for 5 years or less is a reasonable option for relief of vasomotor symptoms
- Evidence supports initiation of HT closer to menopause (healthy arteries respond better than atherosclerotic ones)

Abnormal Uterine Bleeding

“When we fix the plumbing, the bleeding stops”
Magnitude of the Problem

- #1 reason for Urgent hospital admissions for adolescents
- Accounts for 1/3 of all outpatient GYN visits
- Impacts 50% of menstruating women worldwide
- Results in Hysterectomy for 200,000 women every year

PALM – COEIN
(not a new tropical tree)

- Structural Causes of abnormal uterine bleeding
  - P – Polyps
  - A – Adenomyosis
  - L – Leiomyoma
  - M – Malignancy
PALM - COEIN

- Non Structural causes of abnormal uterine bleeding
  - C – Coagulopathy
  - O – Ovulatory Dysfunction
  - E – Endometrial
  - I – Iatrogenic
  - N – Not Otherwise Classified

Initial Evaluation

- History (Medical, Menstrual, Family, GYN)
  - 13% of women with heavy periods have some variant of von Willebrand disease
- Physical Exam
  - Assessment of hemodynamic stability
  - Pelvic exam to rule out trauma to genital tract, vaginal or cervical lesions
Laboratory testing

- PREGNANCY TEST
- History guides evaluation for hemostatic disorder
  - PT/PTT. Fibrinogen, von Willebrand Factor
- CBC, ABO, Type and Cross
- TSH, Ferritin

O- Ovulatory Dysfunction

- Most common in Adolescence and Perimenopause
- Associated with heavy, irregular bleeding
  - The result of chronic unopposed estrogen
  - Failure of the ovary to secrete Progesterone which prompts cyclic shedding in a normal cycle
AUB and Endometrial Biopsy? PEARLS!

- Age 13-19: Incidence of endometrial cancer is 0.2/100,000
  - Consider if 2 years of AUB+Obesity or failure of treatment (assess compliance!)
- Age 19-39: Consider if patient has risk factors
  - Nulliparity, BMI > 30, HTN, Irregular menstruation or family history of endometrial cancer
- Age 40 – menopause: Endometrial sampling indicated

Fixing The Plumbing
(treatment of acute bleeding)

- IV CEE (Premarin) 25 mg IV q 4-6 hours x 24 hours
- Stops bleeding in 72% of patients in 8 hours
- Add Progesterone after treatment to withdraw endometrium
Fixing the Plumbing II

- Monophasic OCP 35 mcg Ethinyl Estradiol
  - TID for 7 days, BID for 7 days, then daily
  - Give 3 packs, skip placebo pills
  - Median time to cessation is 3 days
- Medroxyprogesterone Acetate (Provera)
  - 20 mg TID for 7 days, then 20 mg QD for 21 days
- Norethindrone Acetate (Aygestin)
  - 10 mg daily for 7 days, then 5 mg daily for 21 days

Fixing the Plumbing III

- Tranexamic Acid
  - Synthetic derivative of Lysine that blocks interaction of Plasminogen with Fibrin and prevents dissolution of fibrin clot
  - Used extensively in CV surgery, Orthopedics, Dental
  - 1300 mg PO TID for 5 days
  - 10mg/kg IV (max 600 mg) every 8 hours
  - Do not use with Combination OCPs
Treatment of Chronic Anovulatory Bleeding

• Medical Therapy preferred over Surgical
• Consider need for contraception
• Combined Hormonal Contraceptives (Pill, Patch, Ring)
• Progestin Therapy (Implants, Injectables, Ingestibles)

• Customize Treatment
  – Combined Hormonal Contraceptives (CHC) increase Factor VIII and von Willebrand Factor
  – In PCOS, CHC improve hirsuitism and acne by decreasing serum Androgens
  – In Perimenopause, Low Dose CHC, Levonorgestrel IUD provide cycle control, endometrial protection and contraception
    • Cyclic progestins treat anovulatory bleeding, but no contraceptive effect
FINAL PEARLS from the Plumber

• Studies on Levonogestrel IUD suggest improvement in AUB and Quality of Life when compared to traditional hormonal therapy

• Endometrial Ablation is not first line therapy for anovulatory bleeding
  – Associated with delayed dx of hyperplasia and cancer due to cervical stenosis and inability to biopsy

• You can never be wrong doing a pregnancy test!

Pap Smears and Pap Apps

Your lifeboat in a sea of algorithms....
Cervical Cancer is a Sexually Transmitted Disease

...that can be eliminated
“In God We Trust
All Others Must Have Data”

- Focus on Recommendations, Rationale and Evidence

Evolution of Standardization of Cervical Cancer Screening

  - Development of evidence based consensus guidelines for management of abnormal pap smears (the Bethesda System)

- 2006
  - Further identified strategies for + HPV and guidelines for adolescents
Evidence, Consensus, Change 2012

- 47 experts representing 23 professional societies
- Reviewed published evidence, research and trials
- New Evidence from analysis of a clinical database from Kaiser Permanente Medical Care
  - 1.4 million women, followed for 8 years
  - Modified or validated prior guidelines
  - Size of database allowed for age based recommendations and f/u of abnormalities

Rationale for New Guidelines

- Cervical Cancer prevention is a process with benefits and harms
- Risk cannot be reduced to zero
- Attempts to achieve zero risk could result in overtreatment
- Optimal prevention strategy: Identify and treat HPV abnormalities most likely to progress to cancer
The Facts....

- HPV is the most common Sexually Transmitted Infection in the United States
  - 79 million Americans infected
  - 14 million new infections every year
  - 18,000 women and 9,000 men will develop HPV related cancers this year in the US
  - 4200 deaths from cervical cancer in the US, 2012
  - Worldwide, 528,000 new cases yearly
    - 266,000 deaths in 2012 sub-Sahara Africa

Cervical Cancer and HPV

- Virtually all Cervical Cancers are attributable to 13 types of HPV (99.7 %)
- First Cancer solely attributed to an infectious agent
- HR HPV 16, 18 account for 70 % of invasive cancer with HPV strains 31, 33, 45, 52 and 58 accounting for another 10%
HPV Infection

- Can be transient in up to 70%
- Infection common in women in early 20s
  - Cleared in an average of 8 – 24 months
- Persistence at 1 and 2 years highly predictive of precancerous cervical changes
  - Risk factors for persistence: cigarette smoking, multiple sexual partners, compromised immune system, +HIV, OCP use.
- Lifetime cumulative risk for women is 80%
  - Most HPV infected women WILL NOT develop significant abnormalities

Current Guidelines on Cervical Cancer Screening

- Key Areas of Focus
  - Frequency of Screening
  - Age specific screening recommendations
  - Age specific guidelines for management of abnormalities
  - Use of Cytology (pap smears) and HPV Co-Testing
Onset and Frequency of Screening (Here comes the Pearls)

• Screening begins at age 21 y/o
• Age 21-29 y/o **Screening** every 3 years: Pap Smear only, **NO** HPV testing
• Age 30 – 65 y/o **Screening** every 5 years: Pap Smear and HPV Co-Testing
• Discontinue Screening age 65y/o
  – If adequate prior screening and no history of prior CIN II+ in last 20 years
• Discontinue Screening following Hysterectomy

Interpretation of Co-Testing

• Pap Smear negative and HPV Positive
  – If HPV 16 or 18 positive, refer for Colposcopy
  – If HPV 16,18 negative, Co-Test 1 year
  – If follow up co-testing is negative (pap and HPV), repeat co-testing in 3 years
• ASC-US, HPV negative
  – Repeat co-testing in 3 years
CONFUSED?

Me too!

www.asccp.org/consensus2012

Mobile and Tablet Apps
$9.99
Cervical Cancer Prevention

- HPV Vaccine Gardasil 9
  - 9 Valent, Types 6,11 (warts) and High Risk Types 16, 18, 31, 33, 45, 52, 58
  - Nearly 100% protective in patients with no prior exposure to HPV
  - Females, Males age 9-26 y/o (target 11-12 y/o)
  - Do not test for HPV before giving
  - 3 injections, 0, 2, and 6 months (ongoing clinical trial with 2 dose regimen of 9 valent HPV vaccine)

Our Responsibility

- Educate our Patients and Parents
  - Top reason given for not vaccinating- “My Provider did not Recommend the vaccine”
  - To date, 33 % of US girls have received all 3 doses

- Be aware of patients perceptions
  - Perception of child as “low risk”
  - Concerns for safety and efficacy
  - Seriousness of HPV infection
Pap Pearls

• Pap Smears reported as negative, but lacking Endocervical Cells, can be managed without early repeat
• Pap Smears reported as Unsatisfactory require repeat, regardless of HPV result
• More strategies use Co-Testing to reduce follow up visits
• Pap smear only strategies are limited to women under age 30

Pap Pearls

• AGC or AGUS = Atypical Glandular Cells
  – Always needs referral for colposcopy (possible endometrial biopsy and ultrasound)
  – Result is associated with cancer in up to 27% of cases
  – COMMON MISTAKE: “AGUS, Negative HPV” misinterpreted as ASCUS, patient told to return in 3 years... (this result could mean endometrial cancer)
Questions?