

## Updated Guidelines for Pap Tests and Hormone Replacement Therapy

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### Conflict of Interest Disclosure

*I have no conflicts and disclose that:*

- *I anticipate referencing the unlabeled / unapproved use(s) of progesterone containing IUDs for the following uses*
  - *Hormone Replacement Therapy*
  - *Treatment of endometrial hyperplasia and cancer*
- *I have no financial interest / affiliation with this commercial entity*



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### Cervical Cancer in the US 2019

- About 13,170 new cases of invasive cervical cancer will be diagnosed
- About 4,250 women will die from cervical cancer
- Cervical cancer was the most common cause of cancer death for American women until the advent of the Pap smear
- Worldwide 500,000 new cases and 274,000 deaths (2018)

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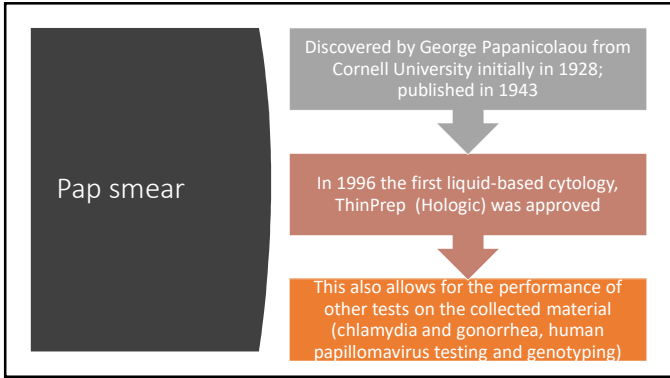
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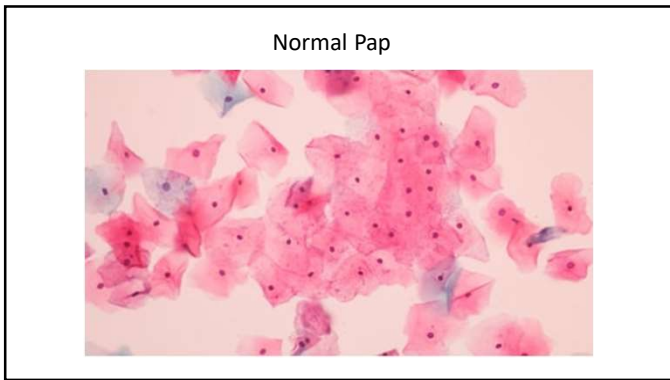
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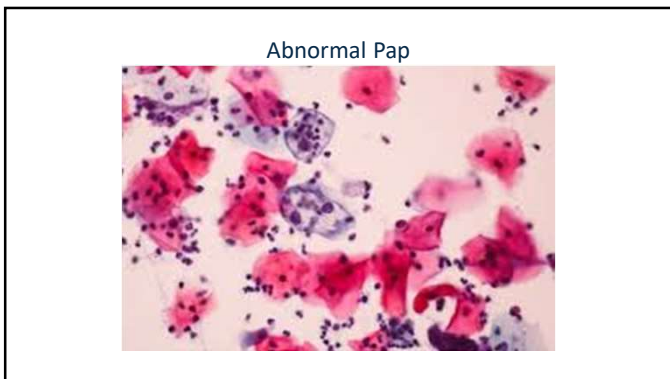
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### Pap Smear Classification

- Original Class 1-4
  - 1 - Normal
  - 2 - Slightly abnormal (infection or mildly pre-cancerous)
  - 3 - Highly suspicious for dysplasia
  - 4- Definitely dysplastic or cancerous

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### Bethesda System

1988 – pathologists decided to get involved in management by recommending treatment.

After they discovered that making recommendations for treatment leads to getting sued. They quickly added the ASCUS (Atypical Squamous Cells of Uncertain Significance) category.

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### Pap Test Results

- NILM Negative for Intraepithelial Lesion or malignancy
- LSIL or LGSIL Low-grade squamous intraepithelial lesion
- HSIL or HGSIL High grade squamous intraepithelial lesion
- Squamous Cell Carcinoma
  
- ASCUS Atypical Squamous Cells of Uncertain Significance
- ASCUS cannot exclude HSIL
- AGC Atypical Glandular cells
  - NOS (not otherwise specified)
  - Neoplastic (suspicious for cancer)
- AIS Adenocarcinoma in situ

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### HPV and Cervical Cancer

- HPV is the most common STD in the US
- HPV has been implicated in 99.7% of squamous cell cervical cancers worldwide
- Adenocarcinomas
  - 89% in women <age 40
  - Only 43% in women >age 60

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### HPV

- There are more than 100 types of HPV, of which at least 14 are cancer-causing (also known as high risk type)
- HPV is mainly transmitted through sexual contact and most people are infected with HPV shortly after the onset of sexual activity.
- Two HPV types (16 and 18) cause 70% of cervical cancers and pre-cancerous cervical lesions.
- HPV infections usually clear up without any intervention within a few months after acquisition, and about 90% clear within 2 years. A small proportion of infections with certain types of HPV can persist and progress to cervical cancer.

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### HPV

- HPV can cause cancer of the cervix, vagina and vulva in women
- HPV can cause cancer of the anus, penis and oropharynx in men.

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### HPV

- It takes 15 to 20 years for cervical cancer to develop in women with normal immune systems. It can take only 5 to 10 years in women with weakened immune systems, such as those with untreated HIV infection.
- Clinical trials and post-marketing surveillance have shown that HPV vaccines are very safe and very effective in preventing HPV infections.
- The HPV vaccine (Gardasil 9) is now approved up to age 45 for both women and men.
- Latest FDA recommendations state that vaccination over age 26 should be a "shared decision" with patient.

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### HPV Vaccine

- Gardasil 9 prevents:
 

• Cervical cancer caused by HPV 16-18	98%
• Vulvar/Vaginal cancer caused by HPV 16-18	100%
• Genital warts (usually HPV 6 and 11)	males 89%
	females 99%
• Anal cancer in men HPV 16-18	90%
• Total prevention of all HPV related cervical cancers	88-97%

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- **Physicians to Parents of New Middle-School Students: Now is the Time for HPV Vaccine (August 2017)**
- Osteopathic physicians encourage parents to get their middle-school age children vaccinated for human papillomavirus virus (HPV), which causes cancers that develop later in life.

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### What is Co-Testing?

- Cytologic Evaluation of Pap test *and* Testing for high risk HPV
- High risk HPV genotypes are 16,18,31,33,35,39,45,51,52,56,58,59,66,and 68
- Highest progression rates to CIN2 or greater are types 16,18 45 and 34

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### Pap smear screening guidelines

- <21 years **No screening**
- Rationale and Evidence. Cervical cancer is rare in adolescents and young women and may not be prevented by cytology screening. The incidence of cervical cancer in this age group has not changed with increased screening coverage over the last 4 decades. Screening adolescents leads to unnecessary evaluation and potentially to treatment of preinvasive cervical lesions that have a high probability of regressing spontaneously and that are on average many years from having significant potential for becoming invasive cancer. This overtreatment, and subsequent increased risk of reproductive problems, represents a net harm.

ASCCP Guidelines

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### Pap Smear Screening Guidelines

- Age 21-29 Every three years with reflex to HPV testing for ASC-US

#### Screening 21-29

- Every 3 years with cytology alone
- High prevalence of HPV
  - Co-testing with HPV should **NOT** be performed
- Annual screening should **NOT** be performed




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### Screening women age 30-65

**Age 30-65.** Testing with cytology alone every 3 years or co-testing with cytology and testing for high-risk HPV types every 5 years.

- Co-testing "preferred" and cytology "acceptable" by all but USPSTF.
  - USPSTF says either acceptable




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### Co-Testing Cheat Sheet

- Pap test ASCUS/HR HPV test negative considered negative
- Pap test ASCUS/HR HPV test positive → colposcopy
- Pap normal HPV positive either repeat one year or test for genotype 16, 18/45
  - 16, 18/45 negative repeat one year.
  - 16, 18/45 positive → colposcopy
- Pap ≥ LSIL needs colposcopy regardless of HR HVP screen
- ASCUS two years in a row regardless of HPV → colposcopy

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### Alternate recommendations Why Five years for Co-Testing >30?

- According to data from Kaiser Permanente Northern California (KPNC) based on screening results from 1,008,855 women, 2734 additional cervical cancer diagnoses and 615 deaths from cervical cancer would be prevented if the three-year co-testing interval is maintained in lieu of the five-year interval

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### Hysterectomy patients without Cervix

- Benign disease – no Paps necessary
- $\geq$  CIN 2 – Every 6 months for a year. Then annually or routine schedule for 20 years depending on severity.

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### When Not to Stop at 65

- History of  $\geq$  CIN 2 should be tested for 20 years even if they have had a hysterectomy.
- Must have had adequate screening (3 negative Paps in the last ten years or two negative co-tests in the last ten years, the latest being within five years)

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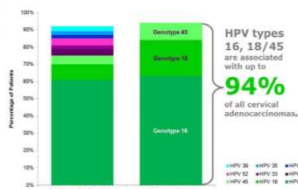
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### Screening age 30-65

- In women  $\geq$  30 yrs co-testing detects 17-31% more CIN3 (precancer) than cytology alone
- HPV testing is superior to cytology for detecting cervical adenocarcinoma
  - Poorer prognosis and incidence is increasing




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ASCCP Guidelines

- The American Society for Colposcopy and Cervical Pathology issues guidelines for the management of abnormal Pap tests.

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Take-home on HPV

- HPV has been implicated in 99.7% of squamous cell cervical cancers worldwide
- The HPV vaccine prevents 88-97% of Cancers caused by HPV including 98% of those caused by HPV 16 and 18, the two most common.

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Take-home on HPV

- HPV affects males too
- Anal and oropharyngeal cancer most common
- Vaccinate males as well as females
- This will also lead to herd immunity

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### Take-home on Pap Tests

- For women's healthcare providers the annual exam is more than just a Pap tests.
- Pap tests are not necessary every year

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### Menopause

- Symptoms of Menopause:
- Anxiety
  - Depression
  - Headache
  - Decreased libido
  - Fatigue
  - Insomnia
  - Hot flashes
  - Irritability
  - Weight gain
  - Osteoporosis
  - Memory lapses
  - Vaginal dryness

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### Menopause

- Definition: The cessation of menstrual periods due to the end of the release of eggs and estrogen by the ovaries.
- Twelve months without a period without another physiologic cause.
- FSH consistently higher than 30

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### What's the Difference Between Menopause and Perimenopause?

- Perimenopause is a place that you pass through.
- Menopause is a destination to which you arrive.

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### Perimenopause

- Perimenopause is related to the quality of the follicle
- Each ovulation is an independent event and the quality of follicle will determine the estrogen and progesterone levels for that cycle
- That can range from normal to low estrogen and normal to no progesterone.
- *So every cycle can be different and hormone levels fluctuate significantly*

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### Perimenopause

- A woman is born with all the follicles she will ever have. In fact they are older than she is.
- So in perimenopause, she is no longer ovulating from the top of the barrel.
- In fact, menopause may be easier to treat than perimenopause because it is largely a static situation.
- Menopausal hormone levels during perimenopause tell you she is in menopause *that day* but things may change the following week.]

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### Perimenopause

- Perimenopause may manifest with irregular and sometimes heavy bleeding.
- Women may have hot flashes and night sweats years before actual menopause and they can be treated.

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### Symptoms of Menopause

- Symptoms of menopause can be divided into two categories
  - Symptoms of estrogen withdrawal
  - Symptoms of estrogen deficiency

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### Symptoms of Estrogen Withdrawal

- Vasomotor (hot flashes, night sweats)
- Interrupted sleep
- Anxiety- palpitations and tachycardia often trigger anxiety

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### Symptoms of Estrogen Withdrawal

- “Brain fog”
- Memory loss
- Depression
- Joint pains

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### Effects of Estrogen Deficiency

- Bone loss – Osteoporosis and fracture
- Vulvo-vaginal atrophy: dyspareunia and urinary urgency

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### Discussion of Menopausal Symptoms

- Menopausal symptoms can have a profound effect on quality of life.
- Patients will often be embarrassed to volunteer symptoms; probably more so to a primary care doctor than a women’s healthcare specialist.

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### Discussion of Menopausal Symptoms

- After questioning about last period to determine time since menopause, bring up the subject, regardless of how many years it has been.
- Hot flashes last an average of 7.4 years although many patients experience the into their 90s.

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### Discussion of Menopausal Symptoms

Ask direct questions:

- Do you have hot flashes or night sweats?
- Do you have increased anxiety or trouble sleeping?
- Do you have decreased lubrication or painful intercourse?
- Do you have urinary urgency (having to go every time you pass a bathroom or hear the water run?)
- Do you get up frequently to urinate at night?

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### Discussion of Menopausal Symptoms

- Legitimize their concerns.
- Let them know that their symptoms are normal and shared by many women.
- Acknowledge that sleep deprivation can lead to many of the traditional symptoms of menopause like irritability and mood swings
- Vaso-motor symptoms may resolve over time but vaginal symptoms will probably not.

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### Supportive therapy

- There are many components of supportive treatment for vaso-motor symptoms. Light, moisture wicking clothing, air conditioning.
- Vaginal dryness can be treated with lubricants, moisturizers and buffering solutions
- Osteoporosis can be prevented with calcium rich diet and weight bearing, bone bending exercise along with many medications.

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Another solution is...

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### Hormone Replacement Therapy

- All patients are not created equal
- All hormone replacement therapy is not created equal

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### History of Hormone Replacement Therapy

- 1942 – Premarin developed by extracting estrogen from Pregnant MAres’ urINe
- 1975 – Post menopausal women on estrogen are discovered to have a four-fold increase in uterine cancer
- Mid 80’s – the addition of progestin to estrogen negates the increase in uterine cancer
- 1986 – 20 million postmenopausal women are on estrogen

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### History of Hormone Replacement Therapy

- 2002 – First results of the Women’s Health Initiative are published in JAMA
- Lead author Jacques Roussouw stated: “this will bring the HRT bandwagon to a halt.”
- 61,000,000 prescriptions written in 2001
- 21,000,000 prescriptions written in 2004

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### The Women’s Health Initiative (WHI)

- One billion dollar government funded study
- Designed to look at cardiovascular and breast cancer risk with conjugated equine estrogen (CEE) and medroxyprogesterone acetate and with CEE alone in hysterectomized women.
- Results: increased risk of cardiovascular disease and breast cancer.
- Stopped early

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### Problems with the WHI

- Studies are designed to look for certain outcomes.
- Because the study was designed to look for an *improvement* in heart disease, the average age patient was 63 years old (average age of menopause 51)
- Because it was a double-blind study, symptomatic patients were excluded because it was felt that symptomatic placebo patients would drop out. 87% of patients completely asymptomatic

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### Problems with the WHI

- The patients were 70% overweight, 34% obese, and 40% smokers
- The HRT used was Prempro which was the most commonly prescribed HRT combination at the time.
- Medroxyprogesterone acetate has a much greater binding ability and bioavailability than progesterone and has been shown to have negative effects on cholesterol, HDL and LDL (HERS trial 1998)

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### Actual WHI Results

- Relative risk of breast cancer in Prempro vs placebo 1.26
- Per the authors “almost reached nominal statistical significance” – ie was not statistically significant
- The placebo group had a lower risk of breast cancer than the treatment group ironically because more of them had taken HRT prior to the study. If you adjusted for that there was no difference

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### Actual WHI Results

- There was no increase in cardiovascular disease at any time if women started HRT prior to age 60.
- This makes sense: Studies in capuchin monkeys from Wake Forest have shown that the benefits of estrogen on deposition of plaque in coronary arteries only occur if hormones are initiated within the equivalent of six years of menopause.

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### Actual WHI Results

- In the estrogen alone arm in women who had a hysterectomy, there was no increase in breast cancer.
- Multiple other studies have shown no increase in breast cancer in women on HRT even in BRCA patients.

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### WHI Politics

- A one billion dollar study demanded results.
- Authors continued to publish follow up studies.
- Negative results made the front page. "Never mind" results were not publicized even when published in the New England Journal

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### Route of Administration

- Vaginal estrogen in local dosage to treat GSM (genitourinary syndrome of menopause) has been shown to have no systemic effects, and not to increase the risk of recurrence in breast cancer survivors.
- ACOG and NAMS approve of its use if non hormonal methods have failed in breast cancer survivors

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### Route of Administration

- Oral but not transdermal preparations of estrogen seem to be associated with venous thromboembolic risk.
- A meta-analysis of observational studies across all ages suggests that, compared with standard-dose oral HT, transdermal HT as well as lower doses of oral or transdermal HT have less effect on risk of VTE

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### Breast Cancer

- The Nurse's Health Study showed no increase in breast cancer in HRT users
- Stage for stage the survival rates are higher for HRT users.
- In 2006 the WHI now reported no increase in breast cancer, even in the E+P group

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Fifteen Years After WHI  
North American Menopause Society

- Estradiol seems to provide more robust anxiolytic and antidepressant effects than CEE
- Low-dose vaginal estrogen preparations are effective and generally safe treatments for VVA even if on tamoxifen or aromatase inhibitor
- Vaginal estrogen reduces the incidence of urinary incontinence (.75) and urinary urgency and reduces recurrent UTI

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Fifteen Years After WHI  
North American Menopause Society

- Hormone therapy effectively prevents postmenopausal osteoporosis and fractures
- Bone protection dissipates rapidly after HT discontinuation, but no rebound in fracture risk has been found.
- Clinical studies of HT in postmenopausal women suggest a benefit on maintaining or increasing muscle mass and related connective tissue, improving strength and improving posttraumatic or post atrophy muscle recovery when combined with exercise

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Fifteen Years After WHI  
North American Menopause Society

- In studies, ET increased epidermal and dermal thickness, increased collagen and elastin content, and improved skin moisture, with fewer wrinkles.
- A meta-analysis of RCTs of women who initiate HT found no increased risk of stroke in women aged younger than 60 years or who were within 10 years of menopause onset.

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Fifteen Years After WHI  
North American Menopause Society

- The attributable risk of breast cancer in women (mean age, 63 y) randomized to CEE MPA in the WHI is less than 1 additional case of breast cancer diagnosed per 1,000 users annually, a risk slightly greater than that observed with one daily glass of wine, less than with two daily glasses, and similar to the risk reported with obesity, low physical activity, and other medications

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Fifteen Years After WHI  
North American Menopause Society

- A 2015 Cochrane review of RCT data found that HT initiated fewer than 10 years after menopause onset lowered CHD in postmenopausal women (RR, 0.52; 95% CI, 0.29-0.96).
- It also found a reduction in all-cause mortality (RR, 0.70; 95% CI, 0.52-0.95)

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Fifteen Years After WHI  
North American Menopause Society

- It remains an individual decision in select, well-counseled women aged older than 60 or 65 years to continue therapy. There are no data to support routine discontinuation in women aged 65 years.

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Fifteen Years After WHI  
North American Menopause Society

- There are indirect economic costs for menopausal women include effects on QOL, work productivity, healthcare resource use, and the potential costs of women who have had a hysterectomy not receiving HT.

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Fifteen Years After WHI  
North American Menopause Society

- Compounded bioidentical HT should be avoided, given concerns about safety, including the possibility of overdosing or underdosing, lack of efficacy and safety studies, and lack of a label providing risks.

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Fifteen Years After WHI  
North American Menopause Society

- Benefits are most likely to outweigh risks for symptomatic women who initiate HT when aged younger than 60 years or who are within 10 years of menopause onset.
- For women aged younger than 60 years or who are within 10 years of menopause onset and have no contraindications, the benefit-risk ratio appears favorable for treatment of bothersome VMS and for those at elevated risk of bone loss or fracture

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Final Pearls

- The WHI was about Prempro, not Hormone replacement.
- Given the differences between E+P and E alone I would suggest that the less progesterone the better
- Although using progesterone cyclically (14 days a month or 14 days every three months) may cause withdrawal bleeding (periods) they are schedulable

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Final Pearls

- Some women hate progesterone
- It may cause bloating and "PMS"
- The use of a progesterone containing IUD, although not FDA approved, seems to have no systemic effects and protects the endometrium completely in European studies.

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Final Pearls

- Newer combinations include CEE plus bazidoxifene, an estrogen modulator that protects the endometrium.
- There is a new product that combines bioidentical oral estrogen and natural progesterone in a continuous combined form.
- Non-oral estrogens come in patches, topical gels, sprays and vaginal rings. Estring is local therapy, Femring is systemic.

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### Hormone Replacement is not 'Natural'

- We hear that menopause is natural. Why treat something natural?
- What's natural is to reproduce and then get out of the way so that younger generations may use the resources to reproduce
- 100 years ago the average female life expectancy was 47. We have extended life artificially so we should offer the hormones to match.

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