Endometrial Hyperplasia and Estrogen Therapy

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“It is astonishing with how little reading a doctor can practice medicine, but it is not astonishing how badly he may do it”

W. Osler
Mt Sopris
Carbondale, CO
Endometrial Hyperplasia

Synonyms

- Simple hyperplasia
- Glandular hyperplasia
- Cystic glandular hyperplasia
- Endometrial hyperplasia
Endometrial Hyperplasia

- Hyperplasia, simple or complex
  - Glandular architecture
  - Glandular crowding at expense of stroma
  - “Back to back” crowding
- Cytological atypia, absent or present
  - Nuclear enlargement
  - Hyperchromasia
  - Irregularity in shape
Hyperplasia Risk Factors

- Anovulation-PCO
- Exogenous estrogen
- Endogenous estrogen
- Family history
- Nulliparity
- Age
- Infertility
- Tamoxifen
- Early menarche
- Late menopause
- Diabetes
- Hypertension
- Granulosa cell tumors
- History of breast of colon cancer
- Menstrual irregularities
Endometrial Hyperplasia
Simple Hyperplasia
Simple Hyperplasia
Simple Hyperplasia
Complex Hyperplasia
Complex Hyperplasia
Hyperplasia with Atypia
Atypical Endometrial Cells
Atypical Glandular Cells
Cystic Hyperplasia
Diagnosis of Hyperplasia
# Evaluation of the Endometrium

<table>
<thead>
<tr>
<th>Options</th>
<th>Pros</th>
<th>Cons</th>
<th>% Sens</th>
<th>% Spec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pipelle</td>
<td>Cheap, office</td>
<td>Disposable</td>
<td>45-100</td>
<td>99</td>
</tr>
<tr>
<td>Vabra</td>
<td>Pain</td>
<td>$, equip, perforation</td>
<td>83</td>
<td>NA</td>
</tr>
<tr>
<td>Curette</td>
<td>Reusable, hysteroscopy</td>
<td>Anesth, perforation</td>
<td>94</td>
<td>NA</td>
</tr>
<tr>
<td>TVS</td>
<td>Cheap, easy, NPV=99%</td>
<td>PPV=9%</td>
<td>80-90</td>
<td>48-80</td>
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</tbody>
</table>
Endometrial Biopsy
Management of Hyperplasia
Management of Atypical Endometrial Hyperplasia

Atypical Endometrial Hyperplasia

Age ≤ 40

D&C ±

Hysteroscopy

Pathology shows cancer

TAH-BSO with lymph nodes

Hysterectomy

Progestogen or Ovulation Induction or Oral Contraceptives

Endometrial evaluation in 3-6 months
Endometrial Hyperplasia

Hyperplasia without atypia
- Patient requests surgical treatment or is unable to take progestins
  - Hysterectomy
- Patient desires to retain uterus
  - Medroxyprogesterone, 10 to 20 mg daily for 11 to 14 days each month
  - Repeat endometrial biopsy in 3 months

Hyperplasia with atypia
- Hysterectomy

Persistent hyperplasia
- Trial of high-dose progestins: medroxyprogesterone, 40 to 100 mg daily for 3 months; repeat biopsy
  - Persistent hyperplasia
  - Hysterectomy

Normal or atrophic endometrium
- Medroxyprogesterone, 5 mg daily for 10 days each month for 12 months; consider annual endometrial biopsy
  - Persistent hyperplasia
  - Hysterectomy
Estrogen Therapy
Steroid Pathway

[Diagram of steroid pathway]
Menstrual Cycle
Effects of Estrogen

Brain
Estrogen helps to maintain body temperature.
Estrogen may delay memory loss.
Estrogen helps to regulate parts of the brain that prepare the body for sexual and reproductive development.

Heart & Liver
Estrogen helps to regulate the liver's production of cholesterol, thus decreasing the build-up of plaque in the coronary arteries.

Ovary
Estrogen stimulates the maturation of the ovaries.
Estrogen stimulates the start of a woman's menstrual cycle – an indication that a girl's reproductive system has matured.

Vagina
Estrogen stimulates the maturation of the vagina.
Estrogen helps maintain a lubricated and thick vaginal lining.

Breast
Estrogen stimulates the development of the breasts at puberty and prepares the glands for future milk production.

Uterus
Estrogen stimulates the maturation of the uterus.
Estrogen helps to prepare the uterus to nourish a developing fetus.

Bone
Estrogen helps to preserve bone density.
Estrogen Replacement During Menopause

**Good effects**
- Strengthens bones
- Lowers LDL cholesterol
- Raises HDL cholesterol
- Reduces menopausal symptoms (e.g., hot flashes)

**Bad effects**
- Increases breast cancer risk
- Increases uterine cancer risk
- Increases blood clot risk
Estrogen Plus Progesterone Replacement

Good effects
- Strengthens bones
- Decreases colon cancer risk
- Reduces menopausal symptoms (e.g., hot flashes)

Bad effects
- Increases invasive breast cancer risk
- Increases heart attacks
- Increases strokes
- Increases blood clots
Estrogen Receptors Trigger Gene Activation

- Estrogen molecule
- Estrogen receptor
- DNA molecule
- Estrogen response elements
- Nucleus
- Cytoplasm
- Coactivators
- Gene activated
- Messenger RNAs
- Specific proteins

Change in cell behavior (e.g., increased proliferation)
Endometrial Stimulation

- Estrogen
  - Cancer Initiated Cells
  - Non-initiated Cells
    - Neoplasia
    - Hyperplasia
Estrogen-Induced Proliferation and Spontaneous New Mutations

Estrogen stimulation

Normal breast cell

Mistake in DNA duplication

Increased proliferation
Antiestrogens

- Estrogen binds to DNA, genes are activated
- Antiestrogen cannot bind to estrogen-bound receptor

Coactivator binds

Binding to DNA
Genes are activated

No gene activation
Tamoxifen as a Cause of Uterine Cancer

- Estrogen
- Tamoxifen

- Estrogen receptor in breast cell blocked
- Breast receptor not activated
- No breast cell proliferation
  - Decreased cancer risk

- Estrogen receptor in uterine endometrial cell
- Uterine receptor activated
- Endometrial cell proliferation
  - Increased cancer risk

National Cancer Institute
The Women's Health Initiative
Randomized Trial

This multi-million dollar, 15-year project, sponsored by the National Institutes of Health (NIH), National Heart, Lung, and Blood Institute (NHLBI), involves 161,808 women aged 50-79, and is one of the most definitive, far-reaching clinical trials of post-menopausal women's health ever undertaken in the U.S.
The Women’s Health Initiative
Randomized Trial

The WHI has two major parts: a randomized Clinical Trial and an Observational Study. The randomized controlled Clinical Trial (CT) enrolled 68,132 postmenopausal women between the ages of 50-79 into trials testing three prevention strategies. If eligible, women could choose to enroll in one, two, or all three of the trial components. The components are:

- Hormone Therapy Trials (HT)
- Dietary Modification Trial (DM)
- Calcium/Vitamin D Trial (CaD)
Effects of Conjugated Equine Estrogen on Stroke in the Women’s Health Initiative

*Circulation.* 2006;113:2425-2434

**Conclusions:** CEE increases the risk of ischemic stroke in generally healthy postmenopausal women. The excess risk appeared to be present in all subgroups of women examined, including younger and more recently menopausal women. There was no convincing evidence to suggest that CEE had an effect on the risk of hemorrhagic stroke.
Venous Thrombosis and Conjugated Equine Estrogen in Women Without a Uterus

Arch Intern Med. 2006;166:772-780.

Conclusion: An early increased VT risk is associated with use of estrogen, especially within the first 2 years, but this risk increase is less than that for estrogen plus progestin.
Conclusions:

Conjugated equine estrogens provided no overall protection against myocardial infarction or coronary death in generally healthy postmenopausal women during a 7-year period of use. There was a suggestion of lower coronary heart disease risk with CEE among women 50 to 59 years of age at baseline.
Conclusions: Treatment with CEE alone for 7.1 years does not increase breast cancer incidence in postmenopausal women with prior hysterectomy. However, treatment with CEE increases the frequency of mammography screening requiring short interval follow-up. Initiation of CEE should be based on consideration of the individual woman's potential risks and benefits.
Conjugated Equine Estrogens and Global Cognitive Function in Postmenopausal Women

JAMA. 2004;291:2959-2968

Conclusion: For women aged 65 years or older, hormone therapy had an adverse effect on cognition, which was greater among women with lower cognitive function at initiation of treatment.
Effects of Estrogen-Alone and Placebo on Disease Rates

Legend:
- CEE
- Placebo
Effect of Estrogen Plus Progestin on Stroke in Postmenopausal Women

*JAMA.* 2003;289:2673-2684

**Conclusions:** Estrogen plus progestin increases the risk of ischemic stroke in generally healthy postmenopausal women. Excess risk for all strokes attributed to estrogen plus progestin appeared to be present in all subgroups of women examined.
Conclusions: Estrogen plus progestin was associated with doubling the risk of venous thrombosis. Estrogen plus progestin therapy increased the risks associated with age, overweight or obesity, and factor V Leiden.
Estrogen plus Progestin and the Risk of Coronary Heart Disease

Conclusions: Estrogen plus progestin does not confer cardiac protection and may increase the risk of CHD among generally healthy postmenopausal women, especially during the first year after the initiation of hormone use. This treatment should not be prescribed for the prevention of cardiovascular disease.
Conclusions: Among postmenopausal women aged 65 years or older, estrogen plus progestin did not improve cognitive function when compared with placebo. While most women receiving estrogen plus progestin did not experience clinically relevant adverse effects on cognition compared with placebo, a small increased risk of clinically meaningful cognitive decline occurred in the estrogen plus progestin group.
Conclusions: More than half of the women with vasomotor symptoms at randomization to active CEE + MPA also reported these symptoms after discontinuing use of the study pills. However, these participants did not include women who were unwilling to be randomized or who had stopped taking the study pills earlier. These findings should be considered when advising women to treat menopausal symptoms with hormone therapy for as short duration as possible. Investigation of alternative strategies to manage menopausal symptoms is warranted.
Conclusions: Relatively short-term use of estrogen plus progestin was associated with a decreased risk of colorectal cancer. However, colorectal cancers in women who took estrogen plus progestin were diagnosed at a more advanced stage than those in women who took placebo.
Effects of Estrogen Plus Progestin on Risk of Fracture and Bone Mineral Density


**Conclusions:** This study demonstrates that estrogen plus progestin increases BMD and reduces the risk of fracture in healthy postmenopausal women. The decreased risk of fracture attributed to estrogen plus progestin appeared to be present in all subgroups of women examined. When considering the effects of hormone therapy on other important disease outcomes in a global model, there was no net benefit, even in women considered to be at high risk of fracture.
Conclusions: Among generally healthy postmenopausal women, conjugated estrogens with progestin did not confer protection against peripheral arterial disease.
Effects of Estrogen plus Progestin on Health-Related Quality of Life

NEJM, March 17, 2003

Conclusions: In this trial in postmenopausal women, estrogen plus progestin did not have a clinically meaningful effect on health-related quality of life.
Disease rates for women on estrogen plus progestin or placebo

<table>
<thead>
<tr>
<th>Disease</th>
<th>Risks</th>
<th>Benefits</th>
<th>Neutral</th>
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<tbody>
<tr>
<td>Heart Attacks</td>
<td>35</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Strokes</td>
<td>35</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>40</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>Blood Clots</td>
<td>15</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>Colon/Rectal Cancer</td>
<td>15</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Hip Fractures</td>
<td>50</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Endometrial Cancer</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Deaths</td>
<td>50</td>
<td>0</td>
<td>50</td>
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Legend:
- Blue: Estrogen + progestin
- Yellow: Placebo
## WHI Summary

<table>
<thead>
<tr>
<th></th>
<th>Estrogen</th>
<th>$E_2$ and MPA</th>
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</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>1.37 (1.09-1.73)</td>
<td>1.31 (1.02-1.68)</td>
</tr>
<tr>
<td>DVT</td>
<td>1.47 (1.06-2.06)</td>
<td>2.06 (1.57-2.70)</td>
</tr>
<tr>
<td>CAD</td>
<td>0.95 (0.79-1.16)</td>
<td>1.24 (1.0-1.54)</td>
</tr>
<tr>
<td>Cognition</td>
<td>1.47 (1.04-2.07)</td>
<td>↓ (p=0.008)</td>
</tr>
<tr>
<td>Vasomotor</td>
<td>NA</td>
<td>50% at DC</td>
</tr>
<tr>
<td>DM</td>
<td>NS</td>
<td>0.79</td>
</tr>
<tr>
<td>CRC</td>
<td>NA</td>
<td>0.56 (0.38-0.81)</td>
</tr>
<tr>
<td>BMD</td>
<td>NA</td>
<td>0.76 (0.69-0.83)</td>
</tr>
<tr>
<td>PVD</td>
<td>NA</td>
<td>0.89 (0.63-1.25)</td>
</tr>
</tbody>
</table>
# WHI Summary

## Gynecological Issues

<table>
<thead>
<tr>
<th>Condition</th>
<th>Estrogen</th>
<th>$E_2$ and MPA</th>
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</thead>
<tbody>
<tr>
<td>Breast Ca</td>
<td>0.80 (0.62-1.04)</td>
<td>1.24 (p&lt;0.001)</td>
</tr>
<tr>
<td>Endometrial Ca</td>
<td>NA</td>
<td>0.81 (0.48-1.36)</td>
</tr>
<tr>
<td>Ovarian Ca</td>
<td>NA</td>
<td>1.58 (0.77-3.24)</td>
</tr>
<tr>
<td>SUI</td>
<td>2.15 (1.77-2.62)</td>
<td>1.87 (1.61-2.18)</td>
</tr>
</tbody>
</table>
Conclusions: Relatively short-term combined estrogen plus progestin use increases incident breast cancers, which are diagnosed at a more advanced stage compared with placebo use, and also substantially increases the percentage of women with abnormal mammograms. These results suggest estrogen plus progestin may stimulate breast cancer growth and hinder breast cancer diagnosis.
Effects of Estrogen Plus Progestin on Gynecologic Cancers and Associated Diagnostic Procedures

*JAMA.* 2003;290:1739-1748

**Conclusions:** This randomized trial suggests that continuous combined estrogen plus progestin therapy may increase the risk of ovarian cancer while producing endometrial cancer rates similar to placebo. The increased burden of endometrial biopsies required to assess vaginal bleeding further limits the acceptability of this regimen. These data provide additional support for caution in the use of continuous combined hormones.
Conclusions: Conjugated equine estrogen alone and CEE + MPA increased the risk of UI among continent women and worsened the characteristics of UI among symptomatic women after 1 year. Conjugated equine estrogen with or without progestin should not be prescribed for the prevention or relief of UI.