Effects of estrogen with and without progestin on urinary incontinence
WHI Trial subgroup. JAMA 2005;293:935-38 (February 23)

Study Type: POE
Purpose: Does menopausal hormone therapy with either estrogen alone versus estrogen + progestin reduce the 1 year incidence and symptom severity of urinary incontinence (stress, urge and mixed)?
Study Duration: 1-year follow-up of the planned 9-year study (was stopped early as published)

Trial Design: This study compare the two arms of the WHI trial – estrogen only arm and estrogen + progestin arm, randomized-controlled, primary prevention trial, multicenter (40 US centers), intention-to-treat, those on hormone therapy were washout before enrollment, those with severe symptoms were excluded, also all patients went through a placebo run-in to assess adherence. Urinary symptoms were self-reported

Drug: 0.625 conjugated equine estrogen vs placebo arm or 0.625 conjugated equine estrogen + medroxyprogesterone 2.5 mg vs placebo arm (2 separate studies are compared)

Patients: n = 27,347 (10,739 patients in estrogen only arm and 16,608 in combination arm), mean age 63 +/- 7 yrs (~45% 60-69, 24% 70-79), 75% white, ~52% were never user’s of HRT; 53% HRT user’s have been using < 5 yrs, 28% have used > 10 yrs; BMI = 30; BP = 130/77; 52% never smoked; 91% had one or more pregnancies; 67% had first child between 20 and 29 yrs of age, 43% had hysterectomy between the ages of 40-49

Inclusion: age 50 to 79; postmenopausal, hysterectomy, staying in residence for 3 more yrs
Exclusion: competing risks with a predicted survival of < 3 yrs; safety (breast cancer, or within 3 yrs, low HCT or platelets); alcoholism; dementia; those with transportation problems

Outcome Events: Change in urinary symptoms on survey – self-reported

1. Are the results valid?
   • Randomized? Yes
   • Double-blinded? Yes
   • Placebo controlled? Yes
   • Were the groups similar? Yes
   • Were patients accounted for? Yes
   • Allocation concealment? Yes

2. What were the results?
   • The incidence was calculated at 1 year.
   • Patients asymptomatic at baseline - N = 5182 in combination hormone and N = 3078 in estrogen only arm

<table>
<thead>
<tr>
<th>Outcome at 1 year in asymptomatic patients at baseline</th>
<th>Hormone</th>
<th>Placebo</th>
<th>ARI</th>
<th>P value</th>
<th>NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress incontinence incidence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination arm</td>
<td>16.0%</td>
<td>8.7%</td>
<td>7.3%</td>
<td>.001</td>
<td>14</td>
</tr>
<tr>
<td>Estrogen only arm</td>
<td>17.4%</td>
<td>8.5%</td>
<td>8.9%</td>
<td>.001</td>
<td>11</td>
</tr>
<tr>
<td>Urge Incontinence incidence</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Combination arm</td>
<td>11.4%</td>
<td>10.8%</td>
<td>0.6%</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Estrogen only arm</td>
<td>13.8%</td>
<td>11.9%</td>
<td>1.9%</td>
<td>.003</td>
<td>53</td>
</tr>
<tr>
<td>Mixed incontinence incidence</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination arm</td>
<td>3.7%</td>
<td>2.8%</td>
<td>0.9%</td>
<td>.01</td>
<td>111</td>
</tr>
<tr>
<td>Estrogen only arm</td>
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<td>3.2%</td>
<td>1.8%</td>
<td>.001</td>
<td>56</td>
</tr>
</tbody>
</table>

3. Will the results help me?
   • The study results are weakened due to the fact that the initial assessment of symptoms was self-reported.
   • The older the patient, the more likely incontinence when using hormones, especially in those > 60 yrs.
   • The longer the use, the more likely incontinence, longer than 5 yrs.
   • The general characteristics of the incontinence worsened on hormone therapy (i.e., amount of urine, frequency)

Conclusion: Hormone therapy does not protect against any form of urinary incontinence, In fact, for every 1000 patients treated with Prempro®, 72 would complain of stress incontinence. Those taking Premain® and no progestin are more likely to have urinary incontinence symptoms than those taking the combination hormone.

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