Plenary Symposium 11

Top Things You Should Know This Year

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Sexual Health Counselor and Educator
Karmanos Cancer Institute
Adjunct Assistant Professor, Department of Surgery
Wayne State University School of Medicine
Detroit, MI
Efficacy of Intravaginal Dehydroepiandosterone (DHEA) on Moderate to Severe Dyspareunia and Vaginal Dryness, Symptoms of Vaginal Atrophy, and of the Genitourinary Syndrome of Menopause

Labrie et al., Menopause, 23 (3), pp. 243-256

Background and Significance

- Vaginal atrophy, epithelial changes at surface of vaginal mucosa associated with increased vaginal pH and changes to lactobacilli → vaginal dryness, dyspareunia, and vaginal irrigation.
- > 60% of post menopausal women experience these symptoms
- DHEA secretion decreases beginning at age 30 → lower androgen and estrogen levels in peripheral target tissues.
- Daily intravaginal DHEA → clinically and statistical benefits on maturation index of vaginal cells, vaginal pH, vaginal dryness, and dyspareunia.

Specific Aim

• To confirm the local benefit of intravaginal DHEA on moderate to severe dyspareunia

Methods

• prospective, randomized, double-blind, and placebo-controlled phase III clinical trial
• n = 1266 enrolled, 463 completed the study; mean age 59.5 years (40-80 years)
• Patients randomized 1:1 to receive daily intravaginal .5% DHEA (6.5mg) or placebo for 12 weeks
• Primary outcomes: % parabasal cells, % superficial cells, vaginal pH, and moderate to severe pain with sexual activity
Results
Compared to placebo, 12 wks of daily insertion of intravaginal DHEA .5%:

- ↓ Parabasal cells by 27.7% (P<0.0001)
- ↑ Superficial cells by 8.4% (P<0.0001)
- ↓ Vaginal pH by 0.66 pH unit (P=0.0002)
- ↑ Vaginal secretions, epithelial integrity, epithelial surface thickness, and color improved by 86%-121% (P<0.0001 all comparisons)
- Serum sex steroids remained within postmenopausal range

Why this Work is Significant

- Confirmed benefits of daily intravaginal DHEA .5% on coprimary objectives
- Systemic estrogen does not consistently treat VA symptoms
- Local estrogen therapy has been limited to superficial layer of vaginal mucosa whereas DHEA:
  - improves density of collagen fibers in second layer
  - stimulates muscular third layer
- Intravaginal DHEA .5% offers an effective modality to treat symptoms and correct physiologically the sequela of vaginal atrophy
Why this work is significant

• Pharmacological blockade of neurokinin B (NKB) signalling with an oral NK3 receptor antagonist improves hot flush symptoms independent of a hormonal effect
• Short proof of concept study
  • Improvements in VMS and physical symptoms (sleep, fatigue, irritability)
  • Twice daily oral administration
  • Well tolerated; 3 patients had transient elevation of transaminases
• Additional study needed


**Aims**

- To investigate the effectiveness of an oral neurokinin 3 receptor antagonist (MLE4901) on menopausal hot flushes.
Methods

- Phase 2, randomized, double-blind, placebo-controlled, single center, crossover trial
- Inclusion criteria: healthy women aged 40-62 years with 7 or more hot flushes/24 hours, some severe or bothersome
- 37 women were randomized; 28 completed the trial and were included in the analysis
- Participants received 4 weeks of MLE4901 (40 mg po twice daily) and placebo in random order separated by 2 week washout
- Primary outcome: total # of hot flushes in the final week of both treatment periods

Results
Results: Greater reduction in total hot flushes in final week of treatment vs placebo

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
<th>On treatment</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>84.54</td>
<td>62.84</td>
<td>21.70</td>
</tr>
<tr>
<td>MLE4901</td>
<td>53.86</td>
<td>20.45</td>
<td>33.41</td>
</tr>
</tbody>
</table>

73% reduction in total hot flush number in final week of 4 week treatment versus placebo.

Greater reduction in hot flush severity, bother and interference vs placebo:

- 41% reduction in hot flush severity
- 45% reduction in hot flush bother
- 58% reduction in hot flush interference

Relative to placebo:

- 41% reduction in hot flush severity: 95% CI -43% (-49 to -35)
- 45% reduction in hot flush bother: 95% CI -45% (-53 to -37)
- 58% reduction in hot flush interference: 95% CI -58% (-70 to -46)

Table 3: Primary endpoint (intention-to-treat analysis, n=37)

Results: Greater reduction in hot flushes severity, bother and interference vs placebo

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo (adjusted mean)</th>
<th>MLE4901 (adjusted mean)</th>
<th>Adjusted estimate of percentage point difference between treatment means</th>
<th>p value comparing adjusted treatment means</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flush</td>
<td>5.69 (5.65 to 5.73)</td>
<td>2.22 (2.20 to 2.25)</td>
<td>-34% (-20 to -49)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hot flush</td>
<td>5.56 (4.96 to 6.17)</td>
<td>2.92 (2.61 to 3.37)</td>
<td>-41% (-36 to -47)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hot flush</td>
<td>5.48 (3.02 to 8.50)</td>
<td>2.16 (1.84 to 2.50)</td>
<td>-45% (-33 to -52)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hot flush</td>
<td>3.98 (2.15 to 3.93)</td>
<td>2.43 (1.97 to 2.88)</td>
<td>-45% (-30 to -55)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hot flush</td>
<td>2.10 (2.04 to 2.10)</td>
<td>1.20 (1.10 to 1.30)</td>
<td>-45% (-33 to -52)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hot flush</td>
<td>1.60 (1.50 to 1.73)</td>
<td>0.60 (0.50 to 0.73)</td>
<td>-45% (-33 to -52)</td>
<td>&lt;0.0001</td>
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Why this work is significant

- Pharmacological blockade of neurokinin B (NKB) signalling with an oral NK3 receptor antagonist improves hot flush symptoms independent of a hormonal effect.
- Short proof of concept study:
  - Improvements in VMS and physical symptoms (sleep, fatigue, irritability).
  - Twice daily oral administration.
  - Well tolerated; 3 patients had transient elevation of transaminases.
- Additional study needed.
Investigator’s Objective

• To assess the association between menopausal hormone therapy (HT) and Alzheimer’s Disease (AD)
Study Design: Prospective Cohort Study with 25-year f/u

- Self-administered questionnaires sent to all women residing in Kuopio Province, Finland: 1989-2009
- Alzheimer’s disease diagnosis based on administrative health records
- Overall N= 8,195, including 227 cases of AD: mean age diagnosis AD: 72.3 years
  - Systemic HT use identified via self-report
  - AD identified from reimbursement data for dementia drugs

Findings suggest short-term use of HT has no impact on AD risk; however, when systemic HT initiated early in menopause and continued long-term, HT may be protective...
HT & Cognitive Function: Other studies

- Three large RCTs found that HT initiated early in menopause and continued for <7 years has no impact on cognitive function
  - WHIMSY (Espeland. JAMA Int Med 2013)
  - ELITE (Mack. Menopause 2014)

- Cache County: long-term prospective cohort Utah study: Initiation of HT early in menopause and continuation for 10+ years: significant reduction in AD risk (Shao. Neurology 2012)

Why This Study is Important:
HT & Dementia: 2017 NAMS PS

- Prevention of dementia should not be considered an indication for use of HT
- Estrogen therapy may have positive cognitive benefits when initiated immediately after early surgical menopause
- Only tentative support (observational studies) is available for a critical window hypothesis of hormone therapy in Alzheimer disease prevention.

JoAnn E Manson, MD, DrPH, NCMP

Chief, Division of Preventive Medicine
Brigham and Women’s Hospital
Professor of Medicine and the Michael and Lee Bell Professor of Women’s Health
Harvard Medical School
Boston, MA

Menopausal Hormone Therapy and Long-Term All-Cause and Cause-Specific Mortality: The Women’s Health Initiative Randomized Trials

*JAMA 2017;318(10):927-938*

Study Aims

• To assess the effects of 5-7 years of menopausal hormone therapy (estrogen + progestin and estrogen-alone, individually and pooled) on 18 year all-cause mortality.

• To examine associations with cause-specific mortality, including deaths from CVD, cancer, and other major illnesses.

• To evaluate whether results differ by age group (50-59, 60-69, 70-79 yrs at baseline).

N=27,347 women
N=7,489 deaths over 18 yrs
(1,088 deaths during the intervention phase; 6,401 post-intervention phase)
### NAMS 2017 Annual Meeting

**Philadelphia Marriott Downtown • October 11–14, 2017**

#### End Points | HR (95% CI) | Favors Hormone Therapy | Favors Placebo | P Value
--- | --- | --- | --- | ---
**Cancer mortality**
- CEE plus MPA vs placebo: 1.06 (0.95-1.18)
- CEE alone vs placebo: 0.99 (0.86-1.13)
- Pooled trials: 1.03 (0.95-1.12)

**Breast cancer mortality**
- CEE plus MPA vs placebo: 1.44 (0.97-2.15)
- CEE alone vs placebo: 0.55 (0.33-0.92)
- Pooled trials: NR

**Colon/rectal cancer mortality**
- CEE plus MPA vs placebo: 1.01 (0.63-1.69)
- CEE alone vs placebo: 1.21 (0.76-1.94)
- Pooled trials: 1.10 (0.82-1.46)

**Other known cancer mortality**
- CEE plus MPA vs placebo: 1.00 (0.84-1.16)
- CEE alone vs placebo: 1.00 (0.84-1.16)
- Pooled trials: 1.00 (0.84-1.16)

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#### End Points | HR (95% CI) | Favors Hormone Therapy | Favors Placebo | P Value
--- | --- | --- | --- | ---
**Alzheimer’s or dementia mortality**
- CEE plus MPA vs placebo: 0.93 (0.77-1.11)
- CEE alone: 0.74 (0.59-0.94)
- Pooled trials: 0.85 (0.74-0.98)

**Accident or injury mortality**
- CEE plus MPA vs placebo: 1.00 (0.73-1.38)
- CEE alone vs placebo: 1.13 (0.72-1.79)
- Pooled trials: 1.04 (0.80-1.36)

**Other known mortality**
- CEE plus MPA vs placebo: 1.00 (0.87-1.15)
- CEE alone vs placebo: 0.91 (0.77-1.07)
- Pooled trials: 0.96 (0.82-1.07)

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**Figure:**

[Graph showing data for end points]
Mortality Outcomes During the Intervention Phase According to 10-Year Age Groups at Randomization

<table>
<thead>
<tr>
<th>Outcome by Age</th>
<th>HR (95% CI)</th>
<th>Favors Hormone Therapy</th>
<th>Favors Placebo</th>
<th>P Value (Trend by Age)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 50-59 y</td>
<td></td>
<td></td>
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<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CEE plus MPA vs placebo</td>
<td>0.67 (0.43-1.04)</td>
<td></td>
<td></td>
<td>0.20</td>
</tr>
<tr>
<td>CEE alone vs placebo</td>
<td>0.71 (0.46-1.09)</td>
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<td>0.04</td>
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<tr>
<td>Pooled trials</td>
<td>0.69 (0.51-0.94)</td>
<td></td>
<td></td>
<td>0.01</td>
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<tr>
<td>CVD mortality</td>
<td></td>
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</tr>
<tr>
<td>CEE plus MPA vs placebo</td>
<td>0.77 (0.33-1.79)</td>
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<td>0.47</td>
</tr>
<tr>
<td>CEE alone vs placebo</td>
<td>0.81 (0.32-2.04)</td>
<td></td>
<td></td>
<td>0.34</td>
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<tr>
<td>Pooled trials</td>
<td>0.79 (0.42-1.47)</td>
<td></td>
<td></td>
<td>0.85</td>
</tr>
<tr>
<td>Cancer mortality</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>CEE plus MPA vs placebo</td>
<td>0.71 (0.38-1.33)</td>
<td></td>
<td></td>
<td>0.37</td>
</tr>
<tr>
<td>CEE alone vs placebo</td>
<td>0.78 (0.43-1.40)</td>
<td></td>
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<td>0.06</td>
</tr>
<tr>
<td>Pooled trials</td>
<td>0.74 (0.48-1.14)</td>
<td></td>
<td></td>
<td>0.05</td>
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<tr>
<td>Other mortality</td>
<td></td>
<td></td>
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<tr>
<td>CEE plus MPA vs placebo</td>
<td>0.53 (0.22-1.27)</td>
<td></td>
<td></td>
<td>0.65</td>
</tr>
<tr>
<td>CEE alone vs placebo</td>
<td>0.51 (0.20-1.26)</td>
<td></td>
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<td>0.02</td>
</tr>
<tr>
<td>Pooled trials</td>
<td>0.52 (0.28-0.97)</td>
<td></td>
<td></td>
<td>0.01</td>
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</tbody>
</table>

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<th>Favors Placebo</th>
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<tr>
<td>Age 70-79 y</td>
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<tr>
<td>All-cause mortality</td>
<td></td>
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</tr>
<tr>
<td>CEE plus MPA vs placebo</td>
<td>1.03 (0.78-1.36)</td>
<td></td>
<td></td>
<td>0.13</td>
</tr>
<tr>
<td>CEE alone vs placebo</td>
<td>1.22 (0.95-1.56)</td>
<td></td>
<td></td>
<td>0.13</td>
</tr>
<tr>
<td>Pooled trials</td>
<td>1.13 (0.94-1.36)</td>
<td></td>
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<td>0.13</td>
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<tr>
<td>CVD mortality</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>CEE plus MPA vs placebo</td>
<td>1.16 (0.74-1.80)</td>
<td></td>
<td></td>
<td>0.14</td>
</tr>
<tr>
<td>CEE alone vs placebo</td>
<td>0.81 (0.55-1.20)</td>
<td></td>
<td></td>
<td>0.14</td>
</tr>
<tr>
<td>Pooled trials</td>
<td>0.95 (0.71-1.27)</td>
<td></td>
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<td>0.14</td>
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<tr>
<td>Cancer mortality</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>CEE plus MPA vs placebo</td>
<td>1.13 (0.73-1.75)</td>
<td></td>
<td></td>
<td>0.15</td>
</tr>
<tr>
<td>CEE alone vs placebo</td>
<td>1.34 (0.90-1.97)</td>
<td></td>
<td></td>
<td>0.15</td>
</tr>
<tr>
<td>Pooled trials</td>
<td>1.24 (0.93-1.66)</td>
<td></td>
<td></td>
<td>0.15</td>
</tr>
<tr>
<td>Other mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CEE plus MPA vs placebo</td>
<td>0.67 (0.35-1.26)</td>
<td></td>
<td></td>
<td>0.15</td>
</tr>
<tr>
<td>CEE alone vs placebo</td>
<td>2.59 (1.36-4.92)</td>
<td></td>
<td></td>
<td>0.15</td>
</tr>
<tr>
<td>Pooled trials</td>
<td>1.35 (0.88-2.00)</td>
<td></td>
<td></td>
<td>0.15</td>
</tr>
</tbody>
</table>
Mortality Outcomes During the 18-Year Cumulative Follow-up According to 10-Year Age Groups at Randomization

<table>
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<tr>
<th>Outcome by Age</th>
<th>HR (95% CI)</th>
<th>P Value (Trend by Age)</th>
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<tbody>
<tr>
<td>Age 50-59 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.97 (0.83-1.14)</td>
<td>.17</td>
</tr>
<tr>
<td>CEE plus MPA vs placebo</td>
<td>0.79 (0.64-0.96)</td>
<td>.18</td>
</tr>
<tr>
<td>CEE alone vs placebo</td>
<td>0.89 (0.79-1.01)</td>
<td>.06</td>
</tr>
<tr>
<td>CVD mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CEE plus MPA vs placebo</td>
<td>0.99 (0.72-1.38)</td>
<td>.45</td>
</tr>
<tr>
<td>CEE alone vs placebo</td>
<td>0.97 (0.65-1.44)</td>
<td>.69</td>
</tr>
<tr>
<td>Pooled trials</td>
<td>0.90 (0.76-1.27)</td>
<td>.77</td>
</tr>
<tr>
<td>Cancer mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CEE plus MPA vs placebo</td>
<td>0.94 (0.75-1.19)</td>
<td>.22</td>
</tr>
<tr>
<td>CEE alone vs placebo</td>
<td>0.83 (0.60-1.14)</td>
<td>.09</td>
</tr>
<tr>
<td>Pooled trials</td>
<td>0.90 (0.75-1.09)</td>
<td>.05</td>
</tr>
<tr>
<td>Other mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CEE plus MPA vs placebo</td>
<td>1.01 (0.75-1.37)</td>
<td>.48</td>
</tr>
<tr>
<td>CEE alone vs placebo</td>
<td>0.63 (0.45-0.89)</td>
<td>.22</td>
</tr>
<tr>
<td>Pooled trials</td>
<td>0.82 (0.65-1.03)</td>
<td>.18</td>
</tr>
</tbody>
</table>

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Conclusions

• Menopausal hormone therapy (HT) for 5-7 years was not associated with risk of long-term all-cause mortality in the overall cohort.

• Among women aged 50-59 at baseline, HT was linked to a 31% lower risk of all-cause mortality, compared to placebo, during the intervention phase of the pooled trials.

• Age differences became attenuated with longer follow-up and were no longer statistically significant.

• All-cause mortality is a “vital” summary measure for the net effect of an intervention on serious and life-threatening health conditions.

• The findings provide support for clinical guidelines endorsing use of HT for management of menopausal symptoms in early menopause (and support guidelines for individualized decision making regarding longer term use).

Gloria Richard-Davis, MD, NCMP, FACOG
Division Director, Reproductive Endocrinology and Infertility
University of Arkansas Medical Sciences
Department of Obstetrics and Gynecology
Little Rock, AR
Background

- Telomeres are the protective caps on the ends of the DNA strands.
- Telomere shortening is involved in all aspects of the aging process on a cellular level.
- Telomere length represents our **biological** age as opposed to our **chronological age**.
- *Many scientific studies have shown a strong connection between short telomeres and cellular aging.*

Study Aims

- To determine whether older women with a history of late maternal age at last childbirth had a longer leukocyte telomere length than those with maternal age at last childbirth of 29 years or less.
A nested case control study was conducted using data from the Long Life Family Study.

387 women who gave birth to at least 1 child and lived to the top 5th % of their birth cohort, or died before the top 5th % of their birth cohort died, but were at least 70 years old.

Logistic regression models using generalized estimating equations were used to determine the association between tertiles of telomere length and maternal age at last childbirth, adjusting for covariates.

Methods

Age at birth of the last child was significantly associated with leukocyte telomere length.

Compared with women who gave birth to their last child before 29 YO, women who were older than 33 YO were two to three times more likely to have leukocyte telomere length in the second and third terciles than in the first tertile.

<table>
<thead>
<tr>
<th>Telomere tertile 2 compared with telomere tertile 1</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age at birth of last child ≤29 y</td>
<td>1.0</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Maternal age at birth of last child: 30-33 y</td>
<td>2.71</td>
<td>(1.17-6.44)</td>
<td>0.019</td>
</tr>
<tr>
<td>Maternal age at birth of last child: 34-37 y</td>
<td>3.36</td>
<td>(1.42-7.93)</td>
<td>0.006</td>
</tr>
<tr>
<td>Maternal age at birth of last child ≥38 y</td>
<td>2.69</td>
<td>(1.09-6.61)</td>
<td>0.032</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Telomere tertile 3 compared with telomere tertile 1</th>
<th>Odds ratio</th>
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<th>P</th>
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<tbody>
<tr>
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<td>1.0</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Maternal age at birth of last child: 30-33 y</td>
<td>2.43</td>
<td>(1.96-6.46)</td>
<td>0.28</td>
</tr>
<tr>
<td>Maternal age at birth of last child: 34-37 y</td>
<td>2.31</td>
<td>(1.02-5.32)</td>
<td>0.044</td>
</tr>
<tr>
<td>Maternal age at birth of last child ≥38 y</td>
<td>3.70</td>
<td>(1.64-8.35)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Results

Table 2: Relation of maternal age at last birth with telomere length: odds of having telomere lengths in the second and third tertiles compared with the first tertile by quartile of maternal age at last birth.

Covariates include: family longevity (yes vs no), length of education (≥12 y vs <12 y), age at blood draw, history of tobacco use (ever vs never), field center (Denmark vs United States), parity (>3 children vs ≤3 children), osteoarthritis, heart disease, stroke, hypertension, diabetes, and cancer.


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Why this work is significant

These findings show an association between longer leukocyte telomere length and a later maternal age at birth of last child, suggesting that extended maternal age at last childbirth may be a marker for longevity.

Suggest a potential genetic basis for reproductive lifespan, longevity and underlying mechanism related to biological aging.

Telomere length does not differ at birth.

Prior research found differences in age and sex-adjusted telomere length.

Oxidative stress shortens telomeres.
Lifestyle Changes May Lengthen Telomeres

Jan L Shifren, MD, NCMP
Director, Midlife Women’s Health Center
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Removal of All Ovarian Tissue versus Conserving Ovarian Tissue at Time of Hysterectomy in Premenopausal Patients with Benign Disease: Study Using Routine Data and Data Linkage

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OBJECTIVE & DESIGN

◆ Determine associations between important health outcomes and bilateral ovarian removal vs. conservation (of at least 1 ovary) at time of hysterectomy in a nationwide study

◆ Health outcomes: ischemic heart disease, cancer, and all-cause mortality

◆ Retrospective analysis of English Hospital Episode Statistics database (hospital admissions) linked to national registers of deprivation indices and deaths

◆ 113,679 women aged 35-45 (premenopausal) who had hysterectomy for benign disease (2004-2014)

◆ Mean length of follow-up 6.2 years

◆ Excluded women with a history of reproductive cancer, including breast
ANALYSIS

◆ Multivariate Cox regression - adjusted for age, ethnicity, comorbidity index (17 medical conditions), and deprivation score (income, employment, health, education, skills, barriers to housing and services, crime, living environment)

◆ **Strengths:** Largest study to date examining this important question, included entire country, comorbidity index and deprivation score available to assess bias/confounding

◆ **Limitations:** Observational study, F/U only 10 years, and no information on HT use, QOL, or impact of BSO beyond age 45 (*closer to age of menopause arguments for ovarian conservation less compelling & NHS did not show protective or harmful effect from BSO in women over age 45*)

RESULTS

◆ In ovarian conservation group c/w BSO group, ischemic heart disease admissions and deaths were significantly lower and time to event significantly longer

◆ In ovarian conservation group c/w BSO group, all deaths were significantly less common and survival time significantly greater
### RESULTS

#### Post-hysterectomy Admissions for Patients with Cancer Diagnosis

<table>
<thead>
<tr>
<th>Cancer diagnosis</th>
<th>Ovarian conservation (n=75,581)</th>
<th>Bilateral removal (n=37,098)</th>
<th>Adjusted HR* (95% CI)</th>
<th>P value (multivariate)</th>
<th>Favours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any cancer</td>
<td>2141 (2.8)</td>
<td>1296 (3.5)</td>
<td>0.8 (0.8 to 0.9)</td>
<td>&lt;0.001</td>
<td>Ovaries conserved</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>784 (1.0)</td>
<td>361 (1.0)</td>
<td>1.3 (1.2 to 1.6)</td>
<td>&lt;0.001</td>
<td>Bilateral removal</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>56 (0.1)</td>
<td>108 (0.3)</td>
<td>0.3 (0.2 to 0.4)</td>
<td>&lt;0.001</td>
<td>(see text)</td>
</tr>
<tr>
<td>Other reproductive CA</td>
<td>69 (0.1)</td>
<td>45 (0.1)</td>
<td>0.7 (0.5 to 1.1)</td>
<td>0.14</td>
<td>Neither</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>90 (0.1)</td>
<td>69 (0.2)</td>
<td>0.7 (0.5 to 0.9)</td>
<td>0.01</td>
<td>Ovaries conserved</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>81 (0.1)</td>
<td>88 (0.2)</td>
<td>0.5 (0.4 to 0.7)</td>
<td>&lt;0.001</td>
<td>Ovaries conserved</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>49 (0.1)</td>
<td>44 (0.1)</td>
<td>0.6 (0.4 to 0.9)</td>
<td>0.01</td>
<td>Ovaries conserved</td>
</tr>
<tr>
<td>Other cancer</td>
<td>1475 (1.9)</td>
<td>906 (2.4)</td>
<td>0.8 (0.8 to 0.9)</td>
<td>&lt;0.001</td>
<td>Ovaries conserved</td>
</tr>
</tbody>
</table>

- In ovarian conservation group c/w BSO group, cancer admissions significantly lower, except for breast cancer

### Why this Work is Significant

- Despite prevention of ovarian cancer with BSO, in ovarian conservation group c/w BSO group, significantly fewer admissions and deaths related to ischemic heart disease or cancer and lower all cause mortality
- Bias/confounding unlikely to explain findings, as ovarian conservation group had more comorbidities and less deprivation than BSO group
- Although HT use after BSO in premenopausal women may reduce risks, women may not receive or continue HT
- Despite consistent findings of improved outcomes with ovarian conservation in premenopausal women undergoing hysterectomy for benign disease and supporting ACOG guidelines, BSO still commonly performed

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Vaginal testosterone cream vs estradiol vaginal ring for vaginal dryness or decreased libido in women receiving aromatase inhibitors for early-stage breast cancer: a randomized clinical trial.


Michelle E. Melisko, MD; Mindy E. Goldman, MD; Jimmy Hwang, PhD; Amy De Luca, BA; Sally Fang, BA; Laura J. Esserman, MD; Amy J. Chien, MD; John W. Park, MD; Hope S. Rugo, MD
Background

• Uncertainty regarding safety and efficacy of available therapies to treat vaginal atrophy (VA) in breast cancer (BC) survivors
• VA affects quality of life, relationship satisfaction, and ability to move on beyond breast cancer.

Study Aims

• To evaluate safety of intravaginal testosterone cream (IVT) or estradiol-releasing vaginal ring (7.5 μg/d) in patients with early-stage BC on aromatase inhibitor.
• Secondary objectives: adverse events and changes in sexual quality of life (QOL), VA, and comparison of serum E₂ assays.

Methods

• prospective, randomized, open-label, noncomparative, single institution phase 2 clinical trial of 2 interventions
• n = 76 enrolled, 69 completed the study; mean age 56 (37-78)
• Patients randomized 1:1 to receive IVT or vaginal ring for 12 weeks
Safety Results: Persistent E2 elevation in 0 patients w/vaginal ring and in a small portion of IVT patients

JAMA Oncol. 2017;3(3):313-319

Intravaginal Testosterone: E2 elevation in 25% at Baseline and 12% at Week 12

Vaginal Ring: E2 elevated in 37% at Baseline and 0% at Week 12

Efficacy Results for Sexual Satisfaction: More improvement in vaginal ring patients

JAMA Oncol. 2017;3(3):313-319
Why this Work is Significant

- AIs associated with significant urogenital atrophy, affecting quality of life and drug compliance.
- Vaginal estrogens are effective tx for urogenital atrophy, but uncertain safety in BC due to potential systemic absorption.
- IVT improves VA in postmenopausal women taking AIs.\(^1\)
- Both vaginal ring and IVT:
  - met protocol-defined primary safety end point for E2
  - improved VA, sexual interest, and desire, while only the vaginal ring improved sexual satisfaction.
- Reasonable to consider using these products for patients using AIs and experiencing urogenital atrophy.

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Preventing Fat Gain by Blocking Follicle-Stimulating Hormone

Wendy M. Kohrt, PhD and Margaret E. Wierman, MD

Preventing Fat Gain by Blocking FSH: Background *(mice)*

- FSH influences thermogenesis and adiposity
- A polyclonal antibody to the beta subunit of FSH diminished ovariectomy-induced bone loss
- This antibody was used in experiments that showed its effect on adiposity


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Preventing Fat Gain by Blocking FSH: Methods

- 3 month old intact mice
- For 8 weeks received intraperitoneal injections with either
  - Goat IgG (control)
  - Polyclonal antibody targeting the beta subunit of FSH (experimental treatment)

UCP1: uncoupling protein 1, uncouples respiration from ATP synthesis and produces heat

CONTROL

No change in adipocytes
No change in resting energy expenditure and bone mineral density

EXPERIMENT

The antibody to FSH prevents FSH from binding to its receptor.
FSH antibody
FSH receptor

Increase in resting energy expenditure and bone mineral density
*Beiging*

UCP1: uncoupling protein 1, uncouples respiration from ATP synthesis and produces heat; *quantitative nuclear magnetic resonance
Preventing Fat Gain by Blocking FSH: Significance?

- That FSH regulates energy homeostasis in mice could have important clinical implications related to accumulation of abdominal fat and associated metabolic changes in menopausal women.
- Prospective cohort studies during the menopause transition observe excess fat gain (abdominal visceral) and decreased energy expenditure.
- Is this due to estrogen loss, aging, or increased FSH?


Preventing Fat Gain by Blocking FSH: Future Directions

Development of a humanized monoclonal antibody that targets the beta subunit of FSH may provide opportunities to determine whether:

- Blocking the actions of FSH can diminish bone loss and fat gain related to menopause?
- Such an antibody would have fewer off-target effects than other pharmacologic therapies which have proved to be problematic in treatment of obesity?