Estrogen therapy after bilateral oophorectomy in premenopausal women

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I have nothing to disclose

Outline of presentation

- Concern about inadequate treatment
  - Application of results from Women’s Health Initiative (WHI) trials to younger women
  - Fear that estrogen may cause cancer
  - Continuing decline in estrogen use (with hysterectomy)
- Premature and early menopause
  - Natural vs. medically induced (primarily surgical)
  - Evidence of increased morbidity and mortality
  - Evidence for the beneficial effects of estrogen therapy
- Concern about unjustified oophorectomies
- Conclusions and recommendations

Sprague et al., Obstet Gynecol 2012; Shuster et al., Maturitas 2010; Faubion et al., Climacteric 2015

Concern about inadequate treatment

- The use of estrogen therapy before the age of natural menopause (50-51 years) is different from the use after the age of natural menopause (WHI data - ET)
- The term estrogen replacement therapy (ERT) should be re-introduced for women experiencing premature or early menopause
  - Premature = before 40 years (1%)
  - Early = between 40 and 45 years (5%)
  - Natural or medically induced (primarily surgical)
- Risk-benefit balance of ERT is clear before age 50-51
- The fear of adverse effects of ERT is unjustified

Vujovic et al., Maturitas 2010; De Vos et al., Lancet 2010; Faubion et al., Climacteric 2015

Ovarian function

Before menopause
- Testosterone
- Androstenedione
- DHEA
- Estrone

After menopause

Somatic targets: reproductive tract, breast, bone, muscle, blood vessels, heart, gut, etc.

Modified from Morrison et al., J. Neurosci 2006
Premature or early natural menopause

- Women with premature or early natural menopause have increased mortality and morbidity
  - Primary ovarian insufficiency (POI)
  - Genetic, autoimmune, other causes
- There are no large-scale randomized trials in these women. We remain uncertain about:
  - Optimal dose (ERT double dose compared to ET?)
  - Route of treatment
  - Problem of fertility (use of oral contraceptive)
- Treat through approximately age 50-51 years or more
  - Treat menopausal symptoms
  - Prevent increased mortality and morbidity

Vujovic et al., Maturitas 2010; De Vos et al., Lancet 2010; Faubion et al., Climacteric 2015

Premature or early surgical menopause

- Concern about unjustified oophorectomies. Justified:
  - With a BRCA1 or BRCA2 genetic variant (35-45 years)
  - With a strong family history of ovarian cancer (unclear ?)
- There are no large-scale randomized trials in these women. We remain uncertain about:
  - Optimal dose (ERT double dose compared to ET?)
  - Route of treatment
  - Most women also underwent hysterectomy
- Treat through approximately age 50-51 years or more
  - Treat menopausal symptoms
  - Prevent increased mortality and morbidity

Vujovic et al., Maturitas 2010; De Vos et al., Lancet 2010; Faubion et al., Climacteric 2015

All-cause mortality

Mayo Clinic Study of Oophorectomy and Aging
Oophorectomy and overall mortality by age

Rocca et al., Lancet Oncology 2006; Shuster et al., Maturitas 2010
Risks vs. benefits of oophorectomy

**BENEFITS**
- Ovarian cancer: ↓80 – 90%
- Breast cancer: ↓50 – 60%

**RISKS**
- All-cause mortality: ↑28%
- Lung cancer: ↑45%
- Coronary heart disease: ↑33%
- Stroke: ↑62%
- Cognitive impairment: ↑60%
- Parkinsonism: ↑80%
- Psychiatric symptoms: ↑50 – 130%
- Osteoporosis and fractures: ↑50%
- Impaired sexual function: ↑40 – 110%

Modified from Shuster et al., Menopausal Medicine 2010

Time frame of deleterious effects

- The deleterious effects of oophorectomy can only be seen after 20 – 30 years of follow-up

Therefore:
- The deleterious effects of oophorectomy have not been seen in short-term follow-up of surgical case series
- The deleterious effects of oophorectomy cannot be studied by clinical trials

Shuster et al., Maturitas 2010; Rocca and Ulrich, Maturitas, 2012; Faubion et al., Climacteric 2015

Age, indication, and ERT

- The younger the woman at time of oophorectomy, the greater the risk of deleterious effects
- The deleterious effects are independent from the indication: prophylactic vs. benign condition
- ERT after oophorectomy can reduce some of the risks: mortality, cardiovascular disease, stroke, and cognitive impairment or dementia
- ERT after oophorectomy does not reduce other risks: anxiety, depression, and parkinsonism

Shuster et al., Maturitas 2010; Rocca and Ulrich, Maturitas, 2012; Faubion et al., Climacteric 2015

Mechanisms of estrogen deprivation

**Oophorectomy**

- Estrogen deficiency

- Accelerated aging: cardiovascular brain, bone, other
- Higher morbidity higher mortality

Non-genetic factors (e.g., smoking or obesity)
- Genetic variants (e.g., APOE or ESR1)

Rocca et al., Molecular and Cellular Endocrinology 2014
Mechanisms of estrogen deprivation

Estrogen deficiency

- Oophorectomy
- Genetic variants (e.g., APOE or ESR1)
- Non-genetic factors (e.g., smoking or obesity)

Estrogen replacement therapy

Accelerated aging: cardiovascular, brain, bone, other

Higher morbidity, higher mortality

ERT and cardiovascular mortality

- Mayo Clinic Study of Oophorectomy and Aging
  - Bilateral oophorectomy at age ≤ 48 years

ERT and risk of cognitive decline or dementia

- Mayo Clinic Study of Oophorectomy and Aging
  - Oophorectomy at age ≤ 48 years

- Estrogen given to age 50 years: HR = 0.8 (0.3 – 2.5), p = 0.69
- Estrogen not given to age 50 years: HR = 1.9 (1.3 – 2.6), p = 0.02

Also confirmed by Bove et al., 2014 – Chicago Study

Conclusions and recommendations, 1

- The majority of women (≈ 98-99%) are at average risk of ovarian and breast cancer, and the risk of bilateral oophorectomy before age 50 years far outweigh the benefits
- The very few women at high risk for ovarian and breast cancer (≈ 1-2%; e.g., with BRCA1 or BRCA2) may consider bilateral oophorectomy before age 50 years, but must be informed of the risk-to-benefit ratio
- If oophorectomy is performed before age 50 years, women should consider taking ERT at least up to age 50-51 years, unless there is a clear contra-indication
**Conclusions and recommendations, 2**

- Women should receive ERT through age 50-51 years, unless
  - History of breast cancer (or estrogen sensitive cancer)
  - Other counter-indication to estrogen (hyper-coagulation risk)
- No large-scale clinical trial. Dose and route remain unknown. Tentative: 100 μg transdermal estradiol
- Unclear what dose would yield blood level comparable to a menstruating woman
- Other hormone therapy, e.g., testosterone
  - Currently not routinely recommended
  - No preparations for women in the US

**Conclusions and recommendations, 3**

- Concern about compliance with ERT
  - Give clear unequivocal message to women
  - Discuss risk-to-benefit balance
  - Discuss the fear of cancer after WHI
- Educate women and gynecologists to avoid unjustified oophorectomies (32% in the US in 2014)
- Bilateral oophorectomy is not a contraceptive procedure and is not a prophylactic option for the majority of women
- We hope that the translation of scientific evidence to practice can be accelerated (less than 17 years!!)

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**Disconnect between scientific evidence and practice**

<table>
<thead>
<tr>
<th>Data and evidence</th>
<th>The gynecologist</th>
<th>The woman</th>
<th>Policy and practice</th>
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</table>

A. Sommer, Getting what we deserve, 2009; Parker, Menopause 2014; Harmanli, Menopause 2014

**Thank you**