HRT Post Hysterectomy for Endometriosis and Supracervical Hysterectomy: What Should We Know?

Cihat ÜNLÜ, M.D.
Acibadem Hospital Bakırköy-Istanbul-Turkey
“No financial relationships to disclose.”
Objective

- Assess the recurrence risk of endometriosis after HRT
- Arrange the timing of HRT after surgery
- Adjust the risk of malignant transformation after HRT
- Choose treatment options in menopausal women with endometriosis
- Assess HRT for supracervical hysterectomy
How science is searching for ways to keep us

Forever Young
HRT

- HRT remains the most efficient treatment to alleviate climacteric symptoms.
- Benefits might be more important than harm in 50-60 year-old women.
- Younger women with surgical menopause or premature ovarian failure may use HRT for many years, until the age that natural menopause would be expected to occur.
Extend of Endometriosis

• In 25% of women undergoing hysterectomy

• 6% of women undergoing routine tubal sterilization

• 2.2% of postmenopausal women have endometriosis and adenomyosis

Concomitant Cancer, Infection and Endocrine Disease Among Endometriosis Patients

<table>
<thead>
<tr>
<th>Cancers (25):</th>
<th>Women with endometriosis, n (%)</th>
<th>Prevalence among women with endometriosis (per 1000)</th>
<th>Estimated prevalence in the general U.S. female population (per 1000)</th>
<th>Prevalence odds ratio</th>
<th>95% CI</th>
<th>P</th>
<th>Sensitivity analysis threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>29 (0.67)</td>
<td>6.70</td>
<td>1.76</td>
<td>3.81</td>
<td>2.60, 5.56</td>
<td>&lt;0.0001</td>
<td>&gt;25 / 75</td>
</tr>
<tr>
<td>Breast</td>
<td>16 (0.37)</td>
<td>3.69</td>
<td>6.82</td>
<td>0.54</td>
<td>0.32, 0.90</td>
<td>0.016</td>
<td>&gt;90 / &gt;90</td>
</tr>
<tr>
<td>Ovary</td>
<td>10 (0.23)</td>
<td>2.31</td>
<td>0.67</td>
<td>3.43</td>
<td>1.74, 6.54</td>
<td>&lt;0.0001</td>
<td>25 / 50</td>
</tr>
<tr>
<td>Non-Hodgkin's lymphoma</td>
<td>2 (0.05)</td>
<td>0.46</td>
<td>0.55</td>
<td>0.84</td>
<td>0.14, 3.37</td>
<td>NS</td>
<td>b</td>
</tr>
<tr>
<td>Infectious diseases:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent upper respiratory infections (26)</td>
<td>1523 (35.17)</td>
<td>351.65</td>
<td>70.14</td>
<td>7.19</td>
<td>6.73, 7.68</td>
<td>&lt;0.0001</td>
<td>&gt;50 / &gt;50</td>
</tr>
<tr>
<td>Candidiasis (27)</td>
<td>1372 (37.65)</td>
<td>376.51</td>
<td>374.88</td>
<td>1.01</td>
<td>0.87, 1.16</td>
<td>NS</td>
<td>b</td>
</tr>
<tr>
<td>Recurrent vaginal infections (28)</td>
<td>1267 (29.25)</td>
<td>292.54</td>
<td>100.00</td>
<td>3.72</td>
<td>3.48, 3.98</td>
<td>&lt;0.0001</td>
<td>50 / 50</td>
</tr>
<tr>
<td>History of mononucleosis (29)</td>
<td>596 (13.76)</td>
<td>137.61</td>
<td>900.00</td>
<td>0.02</td>
<td>—</td>
<td>&lt;0.0001</td>
<td>&gt;90 / &gt;90</td>
</tr>
<tr>
<td>Endocrine diseases:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Addison’s disease (30)</td>
<td>10 (0.23)</td>
<td>2.31</td>
<td>0.09</td>
<td>—</td>
<td>—</td>
<td>&lt;0.0001</td>
<td>b</td>
</tr>
<tr>
<td>Cushing’s syndrome (28)</td>
<td>4 (0.09)</td>
<td>0.92</td>
<td>0.00</td>
<td>—</td>
<td>—</td>
<td>&lt;0.0001</td>
<td>b</td>
</tr>
<tr>
<td>Other diseases:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitral valve prolapse (31)</td>
<td>632 (14.59)</td>
<td>184.36</td>
<td>76.19</td>
<td>2.74</td>
<td>2.32, 3.24</td>
<td>&lt;0.0001</td>
<td>25 / 50</td>
</tr>
<tr>
<td>Congenital birth defects (26)</td>
<td>118 (2.72)</td>
<td>27.25</td>
<td>30.00</td>
<td>0.91</td>
<td>0.75, 1.09</td>
<td>NS</td>
<td>b</td>
</tr>
</tbody>
</table>

Gemmill JA et al, Fertil Steril 2010
<table>
<thead>
<tr>
<th></th>
<th>Crude</th>
<th>p value</th>
<th>Stratified only</th>
<th>p value</th>
<th>Stratified and adjusted</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td></td>
<td>OR (95% CI)*</td>
<td></td>
<td>OR (95% CI)†</td>
<td></td>
</tr>
<tr>
<td>Invasive</td>
<td>1.49 (1.34-1.65)</td>
<td>&lt;0.0001</td>
<td>1.53 (1.37-1.70)</td>
<td>&lt;0.0001</td>
<td>1.46 (1.31-1.63)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Clear-cell</td>
<td>3.73 (3.04-4.58)</td>
<td>&lt;0.0001</td>
<td>3.44 (2.78-4.27)</td>
<td>&lt;0.0001</td>
<td>3.05 (2.43-3.84)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>2.32 (1.94-2.78)</td>
<td>&lt;0.0001</td>
<td>2.20 (1.82-2.66)</td>
<td>&lt;0.0001</td>
<td>2.04 (1.67-2.48)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mucinous</td>
<td>1.09 (0.76-1.58)</td>
<td>0.63</td>
<td>1.04 (0.71-1.51)</td>
<td>0.86</td>
<td>1.02 (0.69-1.50)</td>
<td>0.93</td>
</tr>
<tr>
<td>High-grade</td>
<td>1.11 (0.96-1.29)</td>
<td>0.16</td>
<td>1.16 (1.00-1.35)</td>
<td>0.056</td>
<td>1.13 (0.97-1.32)</td>
<td>0.13</td>
</tr>
<tr>
<td>Low-grade</td>
<td>2.02 (1.38-2.97)</td>
<td>&lt;0.0001</td>
<td>2.22 (1.48-3.31)</td>
<td>&lt;0.0001</td>
<td>2.11 (1.39-3.20)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Borderline</td>
<td>1.26 (1.05-1.50)</td>
<td>0.012</td>
<td>1.19 (0.99-1.43)</td>
<td>0.062</td>
<td>1.12 (0.93-1.35)</td>
<td>0.24</td>
</tr>
<tr>
<td>Mucinous</td>
<td>1.27 (0.97-1.67)</td>
<td>0.078</td>
<td>1.19 (0.90-1.57)</td>
<td>0.23</td>
<td>1.12 (0.84-1.48)</td>
<td>0.45</td>
</tr>
<tr>
<td>Serous</td>
<td>1.31 (1.05-1.63)</td>
<td>0.015</td>
<td>1.28 (1.02-1.61)</td>
<td>0.034</td>
<td>1.20 (0.95-1.52)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

OR=odds ratio. *Stratified by age (5 year categories), ethnic origin (non-Hispanic white, Hispanic white, black, Asian, and other). †Stratified by age (5 year categories), ethnic origin (non-Hispanic white, Hispanic white, black, Asian, and other), and adjusted for duration of oral contraceptive use (never, <2 years, 2–4.99 years, 5–9.99 years, ≥10 years), and parity (0, 1, 2, 3, ≥4 children).

Table 3: Association between history of endometriosis and the histological subtypes of ovarian cancer

From the Ovarian Cancer Association Consortium Lancet Oncology 2012
There is a morphological and biological difference

**Normal endometrium**
- Progesterone, estrogen content differs

**Ectopic endometrium**
- Proliferative activity↑

**Menopause causes:**
- Atrophy in normal endometrium
- Whereas ectopic endometrium can persist, even advance.
Menopause in Endometriosis

• May be part of the treatment
  – Medically induced by GnRHa
  – Surgically induced after hysterectomy
    bilateral oophorectomy

• May be a complication of ovarian surgery

• May occur naturally
Definitive Surgery
When all else fails, and childbearing no longer desired

- Traditionally TH-BSO
- Now often performed laparoscopically
- The relative importance of bilateral oophorectomy vs. hysterectomy has been debated
<table>
<thead>
<tr>
<th></th>
<th>Hysterectomy (n=29)</th>
<th>TH-BSO (n=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent Pain</td>
<td>62 %</td>
<td>10 %</td>
</tr>
<tr>
<td>Re-operation</td>
<td>31 %</td>
<td>4 %</td>
</tr>
<tr>
<td>Relative Risk for Pain Recurrence</td>
<td>6.1 (95% CI 2.5-14.6)</td>
<td>1</td>
</tr>
<tr>
<td>Relative Risk for Re-operation</td>
<td>8.1 (95% CI 2.1-31.3)</td>
<td>1</td>
</tr>
</tbody>
</table>
Surgical Menopause

- Patients are relatively young
- Start HRT after Surgery to prevent
  - Urogenital atrophy
  - Loss of libido
  - Bone loss
  - Prevention of cardiovascular disease in early menopause

Palep-Singh et al, Menopause Int, 2009
HRT

Surgical menopause

Disease recurrence

Malign transformation

Urogenital atrophy

Loss of libido

Bone loss
Recurrence during HRT

- The risk of endometriosis recurrence during HRT is not completely defined.
- Theoretically, oestrogen therapy can re-activate the disease, even where there has been apparent surgical removal of all the endometriotic tissue, but the risk appears to be small.
Estrogen threshold theory

- Various tissues differ in their sensitivity to estrogen.

- Calcium metabolism is the most sensitive.

- A dose of estrogen sufficient to provide bone protection would not necessarily be high enough to reactivate endometriosis.

Barbieri RL, 1998
‘E’ or ‘E+P’

- **E+P HRT: oral combined, Estrogen TTS+cyclic MPA**
  - 0-2.4% recurrence of endometriosis
  - 0-4% recurrence of pain

- **Estrogen only: oral or Estrogen TTS**
  - 2% recurrence of endometriosis
  - 6% recurrence of symptoms

Hormone therapy for endometriosis and surgical menopause (Review)

Al Kadri H, Hassan S, Al-Fozan HM, Hajeer A
• There were only two randomized controlled studies that addressed the controversial issue of the use of HRT for women with endometriosis and postsurgical menopause:
  – Fedele 1999
  – Matorras 2002
• From two non-blinded randomized controlled trials;

Hormone replacement therapy for women with endometriosis and post-surgical menopause may lead to pain and disease recurrence.
Higher Recurrence Risk after HRT

- Presence of deep infiltrating endometriosis
- Residual disease on intestine, bladder
- Peritoneal involvement >3cm
- Incomplete surgery for endometriosis (6%)
  - Residual disease despite TH+BSO

Moen et al, Maturitas, 2010; Palep-Singh, Menopause Int, 2009
Timing of HRT after surgery

Pain recurrence

- 7% in early HRT group (within 6 weeks of surgery)
- 20% in late HRT group (after 6 weeks of surgery)

Hickman et al, Obstet Gynecol, 1998

We could recommend commencing HRT shortly after surgery
Risk of malignant transformation

- Oestrogen only therapy has been associated with an increased risk of malignant transformation of ectopic foci (Oxholm, 2007).

- Extragonadal adenocarcinoma may develop after BSO even at sites far from the pelvis (Brunson, 1988)
Tumors arising in endometriosis

- Most commonly endometrioid adenoCa
- Confined to the site of origin
- Predominantly low grade
Treatment Strategies

Avoidance of estrogen-only tx
- In severe & residual disease
- In obesity

Use of continuous combined tx
- Risk of breast CA
- Progesterone intolerance

Use the lowest dose

Use of tibolone
Rationale for the use of tibolone in menopausal women with residual endometriosis

- A tissue-specific progestogenic effect
  - at the ectopic endometrial level

- An estrogenic effect
  - on climacteric symptoms and bone

Markiewicz, 1990
Alternative Symptomatic Menopause Treatments

- Clonidine
- Serotonin re-uptake inhibitors (SSRI)
- Serotonin and nor-adrenalin reuptake inhibitors (SNRI)
- Gabapentin
- Lubricants
- Moisturizers
## Total versus subtotal hysterectomy for benign gynaecological conditions (Review)

Lethaby A, Mukhopadhyay A, Naik R

| No difference in Urinary Bowel Sexual function | Length of operation (11 min) ↓ Amount of blood loss (57 ml) ↓ in subtotal |
Sub-total hysterectomy

- There may be concern that there is a remnant of endometrium in the cervical stump.
- If this is the case, the presence or absence of bleeding induced by monthly sequential HRT may be a useful empirical diagnostic test.

Evidence is lacking to guide HRT prescription following SH and BSO
HRT and Cervical Cancer

- Squamous cell Ca is not estrogen dependent
- HRT have no effect on HPV carriage or replication
- Prolonged use of OC increases the risk of adenoCa of the cervix
- Unopposed estrogen increases the risk of cervical adenoCa (OR:2.7)
- Estrogen metabolite 16α hydroxyestrone acts as a co factor together with oncogenic HPV

Conclusion

• Estrogen based HRT is essential for women with premature menopause until average age of natural menopause
• E+P and tibolone therapies may be safer for hysterectomized and nonhysterectomized women
• Risk of recurrence and malignant transformation may be reduced with E+P or tibolone
April 30th - May 4th, 2014
Titanic Deluxe Hotel, Belek - Antalya / Turkey

TURKISH GERMAN GYNECOLOGY CONGRESS

www.tajev2014.org

- Matorras R, Elorriaga MA, Pijoan JI, Ramón O, Rodríguez-Escudero FJ. Recurrence of endometriosis in women with bilateral adnexectomy (with or without total hysterectomy) who received hormone replacement therapy. Fertil Steril. 2002 Feb;77(2):303-8.