Prophylactic Oophorectomy or Salpingectomy at the time of Hysterectomy

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Mayo Clinic
MIGS Course: Jan, 2016
ONCE IT WAS EASY..

- Ovarian cancer is the deadliest gynecologic cancer
- There is no reliable or effective screening test
- Ovarian function stops at menopause
- 4-14% of ovarian cancer patients have prior pelvic surgery – opportunity for prevention lost

ACOG practice bulletin number 7, September 1999
RESEARCH BRINGS MORE QUESTIONS:

What is the role of the fallopian tube in “ovarian cancer”?  
What is the impact of surgery on ovarian function?  
Beyond reproductive concerns does ovarian function matter?  
STIC lesions, What do they mean?  
How do we protect high risk women from fallopian tube and ovarian cancer? At what cost to their overall health?  
Can we protect low risk women?  
Where is the balance between causing harm and offering protection?
THE FALLOPIAN TUBE AND OVARIAN CANCER

70% of Ovarian Cancers => Serous Histology

Distinct form other OC histologic types:
  - Highest rate of TP53 mutations in solid cancers
  - Advanced stage at dx
  - High recurrence rate

Serous tumors are epithelial in origin – (OSE is mesothelial)

Resemble fallopian tube epithelium

Precursor lesions absent in ovary, present in tube
> 50% OF SEROUS OVARIAN CANCERS ORIGINATE IN TUBE

Reade et al, J Ob Gyn Canada, Feb 2014:133-140
CHANGING LANDSCAPE FOR OC PREVENTION!

We should out the tubes!
Better be thoughtful about removing tubes...
Will you just take out my tubes?
What’s Known about salpingectomy & OC?

Bilateral tubal interruption associated w 34% decrease in OC.

Endometrioid and Serous histology reduced

Cibula et al, Hum Reprod Update 2011, 17: 55-67

Bilateral tubal interruption (all types) associated with 46% decrease in serous OC and PPC,

Tubal excision associated with 63% reduction in serous OC and PPC

Lessard-Anderson et al, Gyn Onc 135, 2014,423-427
POPULATION BASED STUDY: SALPINGECTOMY AND EOC RISK

Danish Case-control study, 13,241 cases EOC w age matched controls.

OR for all EOC with tubal interruption = 0.87 (0.78-0.98)
For Endometrioid histology OR = 0.66 (0.47-0.93)
For Serous histology OR = 0.92 (p = n.s.)
Salpingectomy OR = 0.58 (0.36-0.95)
Age at time of tubal ligation was not significant**

THE FALLOPIAN TUBE: HIGH RISK WOMEN

GOG 199: 2,605 high risk women > 30 years of age

1,030 RRSO

Tubes sectioned at 2-3 mm intervals

Mutation status known for 99.6%

966 met eligibility

1,575 ROCA Screening
## GOG 199: TUBAL NEOPLASIA

<table>
<thead>
<tr>
<th></th>
<th>Total Neoplasia</th>
<th>Invasive CA</th>
<th>STIC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRCA 1 n=326</strong></td>
<td>2</td>
<td>13</td>
<td>15 (4.6%)</td>
</tr>
<tr>
<td><strong>BRCA 2 n=231</strong></td>
<td>2</td>
<td>6</td>
<td>8 (3.5%)</td>
</tr>
<tr>
<td>No Mutation n=403</td>
<td>0</td>
<td>2</td>
<td>2 (0.5%)</td>
</tr>
</tbody>
</table>

Sherman et al, JCO, 32 (2014),3275-3284
Fig 2. Neoplastic lesions arising in fallopian tube. (A) Low-power (×10 magnification) photomicrograph showing transition from benign fallopian tube epithelium composed of uniform columnar cells (far right) to serous tubal intraepithelial cancer. (B) High-power (×20 magnification) view of (A), demonstrating malignant-appearing cells with pleomorphic nuclei. (C) Nodule of invasive high-grade serous cancer with suggested origin from fallopian tube epithelium (×10 magnification). (D) High-power (×20 magnification) view of (C), showing solid sheets of tumor cells with suggestion of irregular gland formation; right side of image shows benign fallopian tube epithelium.
LOW RISK WOMEN: TUBAL NEOPLASIA

522 low risk women, prophylactic salpingectomy:
Serial section of fallopian tubes at 2-3 mm increments

4 cases STIC – 3 fimbria location
TP53 overexpression demonstrated

11 cases atypical mucosa – 2 w TP53 overexpression

Cancer Protection – at A Cost?

Surgical hazards:

79 women treated w TLH vs. 79 treated with sTLH

No significant difference in:

Operative time,
Change in Hgb,
Postoperative hospital stay,
Postoperative return to normal activity,
Complication rate

Morelli et al, Gyn Onc 129 (2013) 448-451
CANCER PROTECTION - AT A COST?

Ovarian Function:

15&15 women, TLH vs. TLHs – No difference in AMH at 4-6 weeks and at 3 mos. post op.

Findely et al, Fert Ster 100 (2013) 1704-1708

- 79&79 women, TLH vs. TLHs – No difference in AMH, FSH, Ovary diameter, Antral follicular count, peak systolic velocity 3 mos. Post-op.

Morelli et al, Gyn Onc 129 (2013) 448-451

- 91&95 women, Myomectomy or TL w or w/o s – No difference in AMH, FSH, AFC, Vascular Index 3 mos. post-op. No change in outcome if extensive soft tissue resection.

CANCER PROTECTION - AT A COST?

CANCER PROTECTION - AT A COST?

Room for Doubt:

Hysterectomy associated with decreased ovarian reserve?

62 & 21 women, hysterectomy (TAH vs. LAVH) vs. control

Pre-op AMH levels $1.8 \pm 1.81$ (H) vs. $1.79 \pm 1.37$ (C)

AMH = $1.69 \pm 1.62$ 1 week p.o.

$1.42 \pm 1.34$ 1 month p.o.

$1.52 \pm 1.72$ 3 months p.o.

$p=0.805$

Lee et al, EJOG & Repro. Bio, 151 (2010) 82-85
CANCER PROTECTION - AT A COST?

Room for Doubt:

80 women with hysterectomy vs. 83 controls.
Baseline AMH 1 vs. 0.7 (“aging” AMH is value ≤ 1.2)
44% (H) vs. 28.9% (C) had “young” AMH profiles
At one year f/u AMH levels 45% lower in hysterectomy group (p=0.001)

Trabuco et al, Reproductive Sciences 21 (supplement) 2014, 101A
OVARIAN FUNCTION BEYOND CHILDBEARING: DOES IT MATTER?
KENTUCKY ULTRASOUND STUDY

7705 postmenopausal women, age >50
Annual transvaginal ultrasound

256 unilocular cysts (3.3%)
49% resolved spontaneously

54.3% - Age 50-60
23.9% - Age > 60

Bailey et al, Gyn Onc, 69, 3-7 (1998)
PARKER MARKOV MODEL

Goal: Predict optimal strategy for maximizing survival in 40-80 year old women undergoing hysterectomy for benign disease:

- ovarian cancer
- coronary heart disease
- osteoporosis – hip fracture
- stroke & ERT
- breast cancer
- surgical mortality
## IF HYSTERECTOMY
### AGE 50-54

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Proportion Alive at 80</th>
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<tbody>
<tr>
<td>Ovary conserved, No ERT</td>
<td>62.46</td>
</tr>
<tr>
<td>Oophorectomy, No ET</td>
<td>53.88</td>
</tr>
<tr>
<td>Ovary conserved, ET</td>
<td>62.75</td>
</tr>
<tr>
<td>Oophorectomy, ET</td>
<td>62.15</td>
</tr>
</tbody>
</table>
PARKER CONCLUSIONS

Women younger than 65 clearly benefit from ovarian conservation.

At no age is there a survival benefit from oophorectomy.

After age 65 the effect of oophorectomy on survival becomes neutral.
ROCCA COHORT STUDY

1950 – 1987

Olmsted County women

at least 40 years old by Jan 1, 2002

1433 women – Unilateral Oophorectomy

1824 women – Bilateral Oophorectomy

(all surgery was before menopause or before age 56)
THE MAYO CLINIC COHORT STUDY
W. ROCCA, B. GROSSARDT, M. ANDRADE, G. MALKASIAN, J MELTON
LANCET ONCOLOGY, NOV. 2006

1,433 women
Unilateral Oophorectomy
1,274 in study
970 Alive
304 deceased

1,824 women
Bilateral Oophorectomy
1,091 in study
731 Alive
356 deceased
595 postmenopausal
112 due to cancer

2,390 referent women
2,383 in study
1,755 Alive
610 deceased
ROCCA COHORT STUDY

1091 assessable women w BSO
49% “prophylactic” oophorectomies
Median follow-up 25 years

2383 Referent women
95 ultimately had BSO or USO -> censored
Median follow-up 26.4 years
ROCCA COHORT STUDY

No survival difference for all oophorectomies at any age:  \((HR\ 1.05\ (0.92-1.2),\ p=0.45)\)

Statistically significant increased risk of death if prophylactic oophorectomy at <45 years:  \((HR\ 1.67\ (1.16-2.40)\ p=0.006)\)

Increased risk if no ERT and PO at < 45 years:  \((HR\ 1.96\ (1.28-3.01)\ p=0.002)\)

Increase risk if benign indication for oophorectomy and no ERT  \((HR\ 1.54\ (1.14-2.09)\ p=0.005)\)
## Overall Survival: No Change

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Deaths</th>
<th>Hazard Ratio</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Referent</td>
<td>2,383</td>
<td>628</td>
<td>1.00</td>
<td>--</td>
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<tr>
<td>All oophorectomy</td>
<td>1,091</td>
<td>360</td>
<td>1.05</td>
<td>0.45</td>
</tr>
<tr>
<td>Prophylactic oophorectomy</td>
<td>537</td>
<td>184</td>
<td>1.03</td>
<td>0.74</td>
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</table>
# Prophylactic Oophorectomy: Increased Risk Younger Age

<table>
<thead>
<tr>
<th>Age</th>
<th>N =</th>
<th># deaths</th>
<th>Hazard Ratio</th>
<th>P value</th>
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<tbody>
<tr>
<td>&lt; 45</td>
<td>124</td>
<td>33</td>
<td>1.67</td>
<td>0.006</td>
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<tr>
<td>45 - 50</td>
<td>243</td>
<td>75</td>
<td>1.02</td>
<td>0.9</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>170</td>
<td>76</td>
<td>0.9</td>
<td>0.46</td>
</tr>
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</table>
UNDERLYING CAUSE OF DEATH

When all ages are considered - no significant increase in any cause of death:

- Cancer: \( HR=1.28, \ p=0.09 \)
- Vascular: \( HR=0.84, \ p=0.25 \)
- Neurologic: \( HR=1.04, \ p=0.89 \)
- Respiratory: \( HR=0.79, \ p=0.49 \)
- Other: \( HR=1.19, \ p=0.38 \)
UNDERLYING CAUSE OF DEATH

If prophylactic oophorectomy performed before age 45 - risk of death significantly increased for:

- ER Cancer: HR=3.37, p=0.009
- All non-cancer: HR=1.85, p=0.009
- Neuro/Mental: HR=6.28, p=0.003
LIFE EXPECTANCY: AGE AT ESTROGEN DEFICIENCY
LIFE EXPECTANCY: AGE AT ESTROGEN DEFICIENCY

**Graph B**
- 45-50 years
- Referent
- Oophorectomy

**Graph C**
- >50 years

<table>
<thead>
<tr>
<th>Time after oestrogen deficiency (years)</th>
<th>184*</th>
<th>170</th>
<th>123</th>
<th>62</th>
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<tbody>
<tr>
<td>185</td>
<td>173</td>
<td>120</td>
<td>51</td>
<td></td>
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<table>
<thead>
<tr>
<th>Time after oestrogen deficiency (years)</th>
<th>273</th>
<th>248</th>
<th>140</th>
<th>58</th>
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<tbody>
<tr>
<td>273</td>
<td>261</td>
<td>147</td>
<td>71</td>
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</table>
CONCLUSIONS

Prophylactic Oophorectomy decreases the risk of ovarian cancer in low risk women.

For women < 45 years there appear to be health risks that outweigh the advantage of ovarian cancer protection.

The nature of some of the health risks were unexpected.
SUBSEQUENT STUDIES

Clarify risk for cardiovascular disease
Clarify nature of neurologic and mental disorders
CARDIOVASCULAR DISEASE AND OOPHORECTOMY

Annual Deaths among US women:

Cardiovascular disease: 326,900 deaths
Stroke: 86,900 deaths
Ovarian cancer 14,700 deaths

Controls included women with hysterectomy - Possible under-estimate of effect.
Among women having a simple hysterectomy for benign disease, the death rates were:

- 527 per 100,000 if ovaries preserved
- 648 per 100,000 if ovaries removed

For Every 24 women having a BSO, at least one will die prematurely as a result of the oophorectomy
OOPHORECTOMY AND MEMORY

Oophorectomy cohort:
• 813 USO
• 676 BSO

Referent cohort: 1,472 age matched

Direct or proxy interviews using validated dementia questionnaire.

Rocca et. al, Neurology, 2007;69:1074-1083
OOPHORECTOMY AND MEMORY

Figure 2: Cumulative incidence of cognitive impairment or dementia in women with any oophorectomy (A), unilateral oophorectomy (B), and bilateral oophorectomy (C) compared with referent women.
OOPHORECTOMY AND MEMORY

Overall 46% increase in memory impairment with oophorectomy.

Highest risk in women with USO age < 34 (HR 4.03)

If BSO before age 48 HR = 1.62

Risk reduced to baseline if estrogen replacement used until age 50 (in BSO group)
OOPHORECTOMY AND PARKINSONISM

Oophorectomy cohort:

- 1,252 USO
- 1,075 BSO

Referent cohort: 2,368 age matched women

Telephone screen followed by examination for screen + women

Proxy screen if incapacitated or deceased

Medical records / National Death Index review
OOPHORECTOMY AND PARKINSONISM
OOPHORECTOMY AND PARKINSONISM

Overall 68% increased risk if USO or BSO

- Highest risk group: USO at age < 34 (HR 2.9)
- Higher risk if hysterectomy w USO
- If BSO < age 43 HR = 2.17

ERT not protective

Rocca et. al., Neurology, 2007, 69:
OOPHORECTOMY AND MOOD DISORDERS

Bilateral Oophorectomy associated with:

- Increased risk of depression symptoms: HR 1.54 (1.04-2.26)
- Increased risk for anxiety symptoms: HR 2.29 (1.33-3.95)
- Symptoms persisted for years after surgery

ERT not protective
Nurses Health Study
Parker et al, Obstetrics and Gynecology, 2009, 113:1027-1037

16,345 hyst w BSO vs. 13,035 hyst w ovarian conservation

Following BSO:

- Total Mortality HR 1.12
- Fatal / non-fatal CHD HR 1.17
- Stroke HR 1.14
- Breast Cancer HR 0.75
- Ovarian Cancer HR 0.04
- Total Cancer HR 0.90
- Total Cancer Mortality HR 1.17
HORMONES AFTER AGE 55

Menopause is a process... hormone levels decline over time

• Estradiol replaced by low levels of estrone
• Testosterone falls by 49%
• DHEAS declines 77%
• Androstenedione declines 64%
• SHBG increases slightly over time

All changes are exaggerated after oophorectomy....
AS SURGEONS WE HAVE AN OBLIGATION TO:

• Counsel our patients using highest quality evidence.
• Guide decision making toward best outcomes
• Stay abreast of changes in evidence and recommendations
• Question the experts