Opportunistic salpingectomy for ovarian cancer prevention - Jessica N McAlpine, UBC

Disclosures/Conflict of Interest

• No conflicts of interest to declare
• No discussion re off label use and/or investigational drug use

Learning Objectives

1. Understand the role of the FT in ovarian cancer
2. Understand the safety, and cost implications of salpingectomy for ovarian cancer prevention
3. Outline the uptake of salpingectomy and be familiar with the observed and projected impact of the procedure

Ovarian cancer: not 1 disease....
### Ovarian cancer control

<table>
<thead>
<tr>
<th>Screening</th>
<th>Japan</th>
<th>US (PLCO)</th>
<th>UK (UKCTOCS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start up</td>
<td>1985/183,000</td>
<td>1993/78,000</td>
<td>2001/200,000</td>
</tr>
<tr>
<td>Follow-up yrs</td>
<td>9.2</td>
<td>13</td>
<td>8/12+</td>
</tr>
<tr>
<td>Age Median</td>
<td>58</td>
<td>55-74</td>
<td>50-74</td>
</tr>
<tr>
<td>Cancer dx per 10,000</td>
<td>6.5</td>
<td>6.2</td>
<td>6.8 MMS, 5.8 US</td>
</tr>
<tr>
<td>Surgery to cancer ratio</td>
<td>--</td>
<td>20:1</td>
<td>3:1 MMS, 18:1 US</td>
</tr>
</tbody>
</table>

### The role of the fallopian tube in ovarian cancer

- **Fallopian tube as conduit**
  - Tubal ligation (or salpingectomy)
  - Hymen preservation
  - Development of high-grade serous carcinomas

- **Fallopian tube as source**
  - Retrograde menstruation
  - Endometriosis
  - Infection
  - Irritants (e.g., talc)
  - Potential to develop endometrioid/clear cell carcinomas

### Ovarian/peritoneal/fallopian tube ca

Tane, CAHO 2012
Kurman, Am J Surg Pathol 2010
Pakul, 2010
Drapkin, PNAS 2011
While the lifetime risk for ovarian cancer is low in the general population (1.5% overall), the majority of HGSCs arise in this 'average' risk population.

In a retrospective analysis ~20% of ovarian cancer patients had previously had a hysterectomy and 10-15% had previously had a tubal ligation (B.C. Cheryl Brown Ovarian Cancer Outcomes Unit)...an opportunity to have removed the tubes?

Hysterectomy and tubal ligation are two common gynecologic surgeries in which the fallopian tubes have usually been left in place in pre-menopausal women → what would be the impact on ovarian cancer incidence if we removed the fallopian tubes in this population?

**Is there an opportunity for prevention?**

---

**Ovarian Cancer Prevention Educational Campaign (Sept 2010)**

OVCA's clinical team launched a province-wide educational initiative directed at all gynecologists in British Columbia.

Goal: To reduce ovarian cancer by ~40% over the next 20 years

---

**Recommendation to all gynecologists in British Columbia**

**Recommendation**

**Changes in Clinical and Surgical Practice**

- **Goal:** ~40% reduction in ovarian cancer deaths after 20 years

1. Removal of fallopian tube along with fimbriated end at the time of hysterectomy
2. Perform salpingectomy in place of tubal ligation
3. Genetic counseling and BRCA mutation screening in all women with high-grade serous carcinoma

**10-20% through salpingectomy at time of hysterectomy**

10-20% through salpingectomy instead of tubal ligation

10% through risk-reducing surgery in patients with BRCA mutations
SGO Clinical Practice Statement: Salpingectomy for Ovarian Cancer Prevention

November 2013

Salpingectomy may be appropriate and feasible as a strategy for ovarian cancer risk reduction.

A paradigm shift in our understanding …..

Concerns elicited post campaign: a survey of obstetrician-gynaecologists in Canada
Hysterectomy

Hysterectomy alone

pre-campaign

2008

2009

2010

2011

2012

post-campaign

2013

2014

2015

Figure 1: Hysterectomy without oophorectomy in British Columbia

Figure 2: Permanent and irreversible contraception in British Columbia

Short-Term Perioperative:
Operating Room Time

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Hysterectomy n=8365</th>
<th>Hysterectomy with bilateral salpingectomy n=3670</th>
<th>Hysterectomy with BSO n=8904</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR time, mean minutes (SD)</td>
<td>117 (48)</td>
<td>133 (50)</td>
<td>140 (54)</td>
</tr>
<tr>
<td>p-value</td>
<td>control &lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Tubal ligation n=13719</th>
<th>Salpingectomy as sterilization n=1569</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total OR time, mean minutes (SD)</td>
<td>62.0 (34)</td>
<td>72.2 (14)</td>
</tr>
<tr>
<td>p-value</td>
<td>control</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Mean 16 minutes additional time as compared to hysterectomy
Mean 10 minutes additional time as compared to tubal ligation
Short-Term Perioperative: Length of stay

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Hysterectomy</th>
<th>Hysterectomy with bilateral salpingectomy</th>
<th>Hysterectomy with BSO</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOS, mean days (SD)</td>
<td>2.52 (3.0)</td>
<td>2.27 (3.4)</td>
<td>3.04 (3.3)</td>
</tr>
<tr>
<td>p-value</td>
<td>control</td>
<td>0.010</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Shorter LOS associated with hysterectomy with BS and salpingectomy as sterilization

Short-Term Perioperative: Readmission

Age adjusted odds ratios (aOR)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>OR adjusted for age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hysterectomy</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Hysterectomy with bilateral salpingectomy</td>
<td>0.91 (0.75, 1.10)</td>
</tr>
<tr>
<td>Hysterectomy BSO</td>
<td>1.24 (1.16, 1.33)</td>
</tr>
<tr>
<td>Tubal ligation</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Salpingectomy for sterilization</td>
<td>0.85 (0.76, 1.23)</td>
</tr>
</tbody>
</table>

No increased risk of hospital readmission with addition of salpingectomy to the procedure (increased risk with hyst BSO)

Short-Term Perioperative: Blood Transfusion

Age adjusted odds ratios (aOR)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>OR adjusted for age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hysterectomy</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Hysterectomy with bilateral salpingectomy</td>
<td>0.86 (0.67, 1.10)</td>
</tr>
<tr>
<td>Hysterectomy BSO</td>
<td>1.09 (0.90, 1.33)</td>
</tr>
<tr>
<td>Tubal ligation</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Salpingectomy for sterilization</td>
<td>0.77 (0.58, 1.02)</td>
</tr>
</tbody>
</table>

No increased risk of blood transfusion with addition of salpingectomy to the procedure
Hysterectomies and salpingectomy by surgical approach

Cost effectiveness

Costs and Benefits of Opportunistic Salpingectomy as an Ovarian Cancer Prevention Strategy

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Discounted Costs</th>
<th>Life Expectancy Gain (y)</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hysterectomy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>$11,206.52 ± 29.81</td>
<td>21.10 ± 0.03</td>
<td>Dominated</td>
</tr>
<tr>
<td>With O</td>
<td>$11,044.32 ± 1.56</td>
<td>21.12 ± 0.02</td>
<td>---</td>
</tr>
<tr>
<td>With BSO</td>
<td>$12,626.84 ± 13.11</td>
<td>20.95 ± 0.03</td>
<td>Dominated</td>
</tr>
<tr>
<td>Surgical sterilization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tubal ligation</td>
<td>$9,339.48 ± 26.74</td>
<td>22.43 ± 0.02</td>
<td>--</td>
</tr>
<tr>
<td>OS</td>
<td>$9,719.52 ± 3.74</td>
<td>22.45 ± 0.02</td>
<td>$27,278</td>
</tr>
</tbody>
</table>

Future/Ongoing Research
Future/Ongoing Research:

1. The effectiveness of the 2010 educational campaign in increasing the rates of BRCA1/2 mutation referrals.
2. Cohort study examining onset of menopause following tubal ligation and salpingectomy for sterilization.
3. A broader and more comprehensive safety assessment.
4. Effectiveness of opportunistic salpingectomy in preventing ovarian cancer.

Data sources

Objective 1: BRCA1/2 testing

We will examine:

1) referrals to the Hereditary Cancer Program following a diagnosis of HGSC;
2) rates of women undergoing index or carrier BRCA1/2 testing;
3) uptake of risk reducing surgeries and other preventive interventions among BRCA1/2 mutation carriers.
Objective 2: Ovarian function

Cohort study:
- Identify women who had salpingectomy for sterilization or tubal ligation for sterilization in 2010, 2011, 2012 at age 37 or older
- Contact them in 2017 to ask about last menstrual period, duration of time between menstrual periods and menopausal symptoms
- Need 150 women in each group to detect a 2 year difference in onset of menopause by the end of 2017 at α=0.05 and 80% power

Salpingectomy does not impact ovarian reserve when added to laparoscopic hysterectomy*

<table>
<thead>
<tr>
<th></th>
<th>Laparoscopic Hysterectomy</th>
<th>Standard TLH (group B, n=79)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46.8±/–3.4</td>
<td>46.5±/–2.9</td>
<td>0.30</td>
</tr>
<tr>
<td>8. Anti-Mullerian Hormone (ng/mL)</td>
<td>-0.08+/–0.1</td>
<td>-0.18+/–0.1</td>
<td>0.35</td>
</tr>
<tr>
<td>9. Saline aspirating fluid volume (ml)</td>
<td>1.48+/–1.1</td>
<td>1.00+/–0.8</td>
<td>0.15</td>
</tr>
<tr>
<td>10. Antral follicle count</td>
<td>-0.27+/–0.16</td>
<td>-0.14+/–0.1</td>
<td>0.09</td>
</tr>
<tr>
<td>11. Micronodule count</td>
<td>-0.05+/–0.8</td>
<td>-0.19+/–0.6</td>
<td>0.87</td>
</tr>
<tr>
<td>12. Peak systolic velocity (cm/s)</td>
<td>-0.11+/–1.9</td>
<td>-0.19+/–1.0</td>
<td>0.88</td>
</tr>
</tbody>
</table>

* Also no difference in operative time, postoperative hospital stay, postoperative return to normal activity, complication rate (3%)

Objective 3: Extend previous safety assessment

Using the dataset, we will compare our cases and controls according to
1. Serious Adverse Events from Gynecologic Surgery during the hospital stay
   - Death rate
   - Blood transfusions
   - Length of hospital stay
2. Adverse Events from Gynecologic Surgery in the 6 months post surgery
   - Hospital readmissions
   - Physician visits pertaining to gynecologic surgery
   - Post-surgical infections (from diagnostic codes)
   - Diagnostic codes indicating need for pharmacologic pain relief
   - Number of prescriptions filled for an antibiotic or pain killer following surgery
3. Earlier age at menopause
   - Time to initiation on Hormone Replacement Therapy
Objective 4: Effectiveness of opportunistic salpingectomy

- Requires follow-up to the end of 2019.
- Measure rates of ovarian ca and histotype distribution

Hypothesis: Women who have undergone OS will have significantly decreased risks for ovarian cancer, controlling for years of oral contraceptive use, parity, and other confounders.

Why should we be encouraged? Potential impact on ovarian cancer prevention?

TL data: 10,000 ovarian ca cases (7900 invasive, 2200 borderline) from 13 population-based case-control studies

- Tubal ligation reduces the risk of ovarian cancer:
  - Protective effect is **subtype-specific**:
    - Greatest risk reduction observed in clear cell (OR 0.52) and endometrioid (OR 0.48) ovarian cancers
    - Protective, but less so for serous carcinomas (OR 0.81)

Siehl, Salvador et al., Int J Epi, 2013

Mayo Cohort: historical series

- "Excisional" Techniques vs "No Tubal & Non-Excisional Techniques"
Any previous salpingectomy: HR=0.65, 95%CI=0.52-0.81
Bilateral salpingectomy: HR=0.35, 95%CI=0.17, 0.73

Tubal ligation and salpingectomy and the risk of epithelial ovarian cancer and borderline ovarian tumors: a nationwide case-control study

CECILIE MADSEN, LOUISE BAANDRUP, CHRISTIAN DEHLENDORFF & SUSANNE K. KJER

Bilateral salpingectomy: OR=0.58, 95%CI=0.36-0.85

Effect of tubal sterilization technique on risk of serous epithelial ovarian and primary peritoneal carcinoma

Cecilia R. Lessard-Anderson, Kathryn I. Harding, Rochelle J. Mackay, Sean C. Dory, William A. Ciby, Arien I. Wilairat, Jennifer M. Sassen, Jamie N. Bullock-Carey

Excisional tubal sterilization: OR=0.59, 95%CI (0.29-1.17)

Is there uptake elsewhere in the world?

Global Uptake of Opportunistic Salpingectomy
Questions/unanswered

- Will Salpingectomy protect from all HGS ovarian cancers? 
  No...
  - Up to 30% of HGSC cases show no evidence of tubal involvement
  - These cancers may originate in:
    - Ovarian surface epithelium (OSE, modified mesothelium)
    - Tubal epithelial cells that become entrapped during disruption of the ovarian surface during ovulation
    - Ovarian-tubal junction

- Role of Essure/tubal blockage by other means?

Summary

Recommendation
Changes in Clinical and Surgical Practice

1. Removal of fallopian tube along with fimbriated end at the time of hysterectomy
2. Perform salpingectomy in place of tubal ligation

Practical Aspects:
- Additional ~10 minutes OR time when bilateral salpingectomy added to hysterectomy
- Additional ~10 minutes for bilateral salpingectomy instead of tubal ligation

Safety:
- No discernible increase in length of stay, hospital readmission or required blood transfusions in women undergoing opportunistic salpingectomy. Subtle or long term Δ need f/u.

Uptake:
- Hysterectomy with OS increased from 8% to 75% between 2008 and 2013
- OS for sterilization increased from 0.5% to 48%

Cost effectiveness:
- OS is cost effective compared to relevant gynaecologic procedures
Acknowledgments

Centre for Translational and Applied Genomics
David G Huntsman
Alicia A Tone (Rose Uni)
Nirit Rosenberg
Michelle Woo

Pathology and Lab Sciences
S Blake Gilks

Statistical/EP Support
Gillian Hanley

International Collaborators:
Malcolm Pike
Leigh Pearce
Rajit Manchanda
Usha Menon

UBC & BCCA Gyn
Dianne Miller
Janice Kwon
Sarah Finlayson
Gavin Stuart
Mark Carey
Mark Heywood
Mariee Law
Paul Holmes
Anna Tinker
Ken Sawmerton
Susan Eldred
Trevor Cohen
Mireille Maggiari
Tom Dikan

UBC & BCRA Gyn
Dianne Miller
Janice Kwon
Sarah Finlayson
Gavin Stuart
Mark Carey
Mark Heywood
Mariee Law
Paul Holmes
Anna Tinker
Ken Sawmerton
Susan Eldred
Trevor Cohen
Mireille Maggiari
Tom Dikan

UBC & BCRA Gyn
Dianne Miller
Janice Kwon
Sarah Finlayson
Gavin Stuart
Mark Carey
Mark Heywood
Mariee Law
Paul Holmes
Anna Tinker
Ken Sawmerton
Susan Eldred
Trevor Cohen
Mireille Maggiari
Tom Dikan