

# Opportunistic Salpingectomy: We Chose to Act, Not Wait

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We are now five years from the initiation of our campaign in British Columbia (BC) to encourage opportunistic salpingectomy (OS) for the prevention of ovarian cancer and approximately four years from the editorials and civilized debate contributed by Dr John Thiel, our team, and Dr Morelli et al. in the *Journal*.<sup>1–3</sup> Ironically, as in 2012, the timing of this editorial coincides with a colourful election campaign in the United States, and the discussion of civility in debate by the *Journal's* Editor-in-Chief<sup>4</sup> remains highly relevant.

The ovarian cancer prevention campaign was stimulated by robust evidence that the majority of the most common subtype of epithelial ovarian carcinomas (high-grade serous) originates in the distal fallopian tube, as summarized in the initial publications.<sup>1–3</sup> The two next most common ovarian cancer histotypes (clear cell and endometrioid) were shown to originate from endometria that had passed through the fallopian tubes into the peritoneal cavity, implanting on the ovaries themselves. Tubal ligations had consistently been shown to reduce the risk of developing ovarian cancer, and it was believed that removal of the fallopian tubes would reduce the risk further. Over their lifetime, many women undergo gynaecologic procedures in which the fallopian tubes are accessible, providing an “opportunity” to remove the tubes if child-bearing has been completed or is no longer desired. Although the lifetime risk of ovarian cancer in the general population is low, it is this low-risk population that provides the majority of new cases of ovarian cancer. Overall survival rates in ovarian cancer have plateaued, and we have no impactful means of early detection or screening. Prevention through removal of the fallopian tubes became a spearhead for action.

In 2010 we sent an educational DVD to all practising gynaecologists in BC and asked them to discuss with their patients removal of their fallopian tubes (“opportunistic salpingectomy”) during hysterectomy, even when the ovaries were being preserved, and as an option for

sterilization in place of tubal ligation (TL). We also recommended that all women with high-grade serous carcinoma should be referred to the hereditary cancer program to undergo counselling and genetic testing for BRCA1/2 mutations, in order to offer screening or risk-reducing options for other BRCA-associated cancers in that individual and as a step towards testing and identifying other possibly affected family members. This initial campaign was supported by the Society of Gynaecologic Oncologists of Canada, with a formal statement in both official languages released in September 2011. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists recommended consideration of bilateral salpingectomy in November 2012 (updated July 2014), and the Society of Gynecologic Oncology in the United States issued a clinical practice statement and guidelines for discussion of bilateral salpingectomy in November 2012. A Committee Opinion from the American College of Obstetricians and Gynecologists was generated in January 2015. Today, a search in an online journal database for the terms “opportunistic,” “risk-reducing,” or “prophylactic” salpingectomy yields over 80 relevant publications from at least a dozen countries. Physician attitudes towards OS, both before<sup>5</sup> and after<sup>6–8</sup> this practice change have been reported and have enabled us to address concerns such as those voiced by Dr Thiel.<sup>1</sup>

In 2014, we published data related to hospital stay, blood transfusion, hospital readmissions, and operating times in 44 000 women undergoing OS over a four-year interval, and found no increase in complications associated with the procedure.<sup>9</sup> Subsequently, other groups have also assessed surgical morbidity with reassuring results.<sup>10,11</sup>

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One of the greatest voiced concerns has been the theoretical impact of OS on ovarian function, knowing that premature menopause is associated with cardiovascular and other morbidities that might negate the proposed benefit of ovarian cancer risk reduction. The groups that have published or have pending publications from RCTs addressing this question have reported no evidence of adverse effects of OS on ovarian function.<sup>11,12</sup> In BC, we are following up on women who underwent bilateral salpingectomy for the purpose of sterilization until the natural age of menopause, measuring rates of amenorrhea and hormonal parameters to see whether these differ from age-matched control patients who underwent TL. Ironically, we believe that the OS campaign is actually prompting physicians to preserve the ovaries more often; they can potentially reduce ovarian cancer risk and still avoid the all-cause mortality associated with oophorectomy at any age.<sup>13</sup>

Cost-analysis modelling that considered perioperative risks, impact on ovarian cancer risk reduction, and morbidities associated with premature menopause secondary to oophorectomy showed that OS with hysterectomy was less costly and more effective than hysterectomy alone; it also reduced the number of cases of ovarian cancer and prolonged average life expectancy. OS for sterilization was considered more costly than TL because of longer operating time and higher complication risk; however, OS was more effective in reducing the risk of developing ovarian cancer. The number needed to treat to prevent the diagnosis of ovarian cancer was acceptable for both scenarios.<sup>14</sup>

What has been most impressive is the uptake of this procedure over the past several years.<sup>9</sup> If we exclude from consideration data on women who undergo hysterectomy with bilateral salpingo-oophorectomy for indications that have not changed over time (e.g., for advanced age or pathology such as cancer), by the end of 2013, 75% of women in BC who underwent hysterectomy had OS compared with just 8% in 2008. For surgical sterilization procedures, fewer than 1% were performed using OS in 2008, but by 2013 almost half (48%) of tubal procedures performed were bilateral salpingectomies. Clearly our community of physicians has accepted our recommendation. If adverse events were being encountered in the community, then we presume that the practice of OS would have stopped. The experience for both physicians and patients has been highly favourable and has gained momentum.

What cannot yet be demonstrated is the impact of OS in BC on ovarian cancer mortality. Because the average age of women undergoing these procedures precedes the average age of onset of ovarian cancer in the general/low-risk community, often by several decades, it will not be

possible to detect a difference in ovarian cancer rates, or histologic distribution, until that cohort “comes of age.” While awaiting this information, we have seen the publication of single institution,<sup>10</sup> case-control,<sup>15,16</sup> and population-based<sup>17</sup> series. A meta-analysis of 3500 women who underwent bilateral salpingectomy, with over 5.5 million control patients, demonstrated a 49% reduction in the risk of developing ovarian cancer.<sup>18</sup> Except for the Rochester Epidemiology Project (where salpingectomy was performed for sterilization),<sup>16</sup> the indication for tubal removal in the other series was not given but was unlikely to be for the explicit purpose of ovarian cancer risk reduction. There may be other factors that influence ovarian cancer risk reduction in these cohorts for which we have not accounted. Thus we look forward to direct evidence, in the cohorts in which the intervention has taken place (i.e., in BC, in Canada, and internationally), of whether this initiative has indeed been successful. We also look forward to measuring and reporting the impact of the recommendation for hereditary cancer referrals for all high-grade serous cancers.

Some jurisdictions remain skeptical and will not consider risk-reducing salpingectomy outside a clinical trial. This issue was debated recently in the *British Journal of Obstetrics and Gynaecology*.<sup>19,20</sup> The debate reiterated the concern about whether we should choose to act now or whether we should wait for definitive proof of benefit. Kehoe, who argued against requiring proof, estimated that waiting 20 years for the results of an RCT would result in 85 000 deaths from ovarian cancer in British women that could possibly have been avoided.<sup>19</sup>

We have chosen to act, not wait. However, we consider it a major responsibility to report on the progress of this intervention with diligence. Multiple research teams have also undertaken the OS strategy and have published their findings, enabling us to provide more information in counselling women today. We are currently able to tell women the following:

1. OS is feasible. Removal of the fallopian tubes at the time of hysterectomy or for permanent contraception is achievable through minimally invasive, laparoscopic, or vaginal approach and is well within the skill set of any gynaecologic surgeon. High uptake has been demonstrated across all geographic areas of BC and Canada, and internationally in both high- and low-resource countries. Additional surgical time for OS is in the range of 16 minutes for hysterectomy and 10 minutes for sterilization. Health economic analyses for OS are favourable.
2. OS is safe. Major perioperative complications have not increased, according to population data in thousands of

women in BC and in smaller international trials. Studies to date on the impact of OS on ovarian function have been reassuring. The follow-up study examining age at onset of menopause following OS for sterilization in the BC patient population is expected to be completed by 2019.

3. The impact of OS on the incidence of ovarian cancer in BC and Ontario will require five more years to be measurable. We estimate we will have data on the effectiveness of OS as an ovarian cancer prevention strategy by 2020 and data on effectiveness within histologic subtypes by 2025. In the meantime, we are encouraged by recently published case-control and population series demonstrating ovarian cancer risk reduction in women who have undergone salpingectomy.<sup>15–17</sup>

We do not suggest that OS will be appropriate for all individuals, nor should it be offered as a stand-alone procedure in low-risk women. Some women will be poor surgical candidates, and many non-surgical alternatives for contraception or management of benign uterine pathology are available. Of all interventions, oral contraceptive use has arguably had the greatest impact in lowering ovarian cancer risk, and appropriate use can be encouraged. Relative contraindications may preclude this option in some older women, and many women may wish to pursue non-hormonal methods of contraception. Ultimately, whether or not a woman undergoes OS remains a decision between her and her physician and requires judgement and common sense. We feel that discussion of OS should be part of informed consent. We continue to strive to “do no harm” but hope we can also go beyond this dictum and “do some good” for these women, enabling them to reduce their risk of developing the most lethal of gynaecologic cancers. In short, we believe that OS “sounded like a good idea at the time” and that it still does.

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