

**Article details:** 2021-0219

**Title:** Opportunistic salpingectomy between 2011 and 2016: a descriptive analysis

**Authors:** Gillian E. Hanley PhD, Jin Niu MSc, Jihee Han MPH, Sharon Fung MSc, Heather Bryant MD PhD, Janice S. Kwon MD, David G. Huntsman MD, Sarah J. Finlayson MD, Jessica N. McAlpine MD, Dianne Miller MD, Craig C. Earle MD

**Reviewer 1:** Dr. Karl Tamussino

**Institution:** Medical University of Graz

General comments (author response in bold)

Abstract

- Do you want to mention in the Abstract that these were hysterectomies for benign indications ("benign hysterectomies")?

**We have rephrased and it reads: "Opportunistic salpingectomy (OS) is the removal of fallopian tubes during hysterectomy for benign indications or instead of tubal ligation." Page 3**

- "jurisdictions": might "provinces" be the better word? {Editorial note: we think jurisdictions is fine, since this also includes the Territories.}

**We have kept jurisdictions as we also include data from the Canadian territories.**

- Interpretation: you could add here that there is considerable variation across Canada.

**We have rephrased the first sentence of the interpretation to read "The uptake of OS is improving but there is considerable variation across included jurisdictions." Page 3**

Introduction

Since this will be read by nongyns you could underline that ovca is the most common cause of gyn cancer death and the 5th leading cause of cancer death overall in women.

**We have added the following "Ovarian cancer is the most lethal of the gynecologic cancers, and fifth leading cause of cancer deaths in females.(1)" Page 4**

- line 26 BC = British Columbia

**We have fixed this throughout the manuscript. We now abbreviate British Columbia after its first use in the manuscript and use BC throughout the rest of the manuscript.**

- You could also underline that Canada (BC in particular) is a pioneer here and that SOGC was the first professional society in the world to officially recommend OS and that many other societies worldwide followed (Ntoumanoglou-Schuiki et al. Eur J Obstet Gynecol Reprod Biol. 2018 Jun;225:110-112). You can be proud of this.

**Thank-you for pointing this out and bringing this paper to our attention. We have added the following sentence to the introduction section "While Canada was the first country to recommend consideration of salpingectomy during benign gynecologic surgery, by 2018 there were nine countries with statements supporting consideration of opportunistic salpingectomy.(15)"**

Results

- I know this is not the subject of the paper but do you have an idea how the numbers/rates of benign hysterectomy developed in your time frame? In many countries benign hysts have been going down.

**Our hysterectomy rate did decrease slightly over the study period, but it was not a clear decreasing trend. Data from table 1 now indicates that total hysterectomies performed were 30,914 in 2011 and 29,276 in 2016, but the year-to-year change was to decrease in 2012, stay relatively stable in 2013, increase slightly in 2014, decrease again in 2015 and increase slightly in 2016, thus there was not a clear trend of decreasing use of benign hysterectomy in our study population.**

- Do you have data on the approaches to benign hysterectomy (open, laparoscopic, vaginal, robotic) and whether this might have influenced the rate of OS? If not you could discuss this as a limitation.

**We were unable to analyze by surgical approach. We have added the following to the discussion section “Fourth, we were unable to study uptake of OS by surgical approach, and thus cannot present data on how variation in use of alternative surgical approaches (i.e. robotic, open, laparoscopic or vaginal) could have influenced uptake of OS.” Page 13**

Discussion

A number of studies from the US and elsewhere have looked at uptake of OS/PBS. You could cite and discuss these briefly.

**While we did consider presenting international data, because this is a Canadian paper for a Canadian audience and due to the word limit, we have decided to keep the focus on Canada.**

- A limitation is that this ends in 2016, which is already a while back. Things may have picked up since then.

**Yes, we have added this to the limitations section. It now reads “First, we are limited by the fact that our data extend only until 2016. Given that there was a trend of increasing uptake across many jurisdictions, it is likely that rates of OS are currently higher in many, and possibly all, jurisdictions studied. However, given the change between 2011 and 2016, and the fact that these data include two full calendar years following the SOGC recommendation for OS, we expect the trends reported are still relevant.” Page 12**

Congratulations!

**Reviewer 2:** Dr. James Bentley

**Institution:** IWK Health Centre, QEII Health Sciences Centre Foundation

General comments (author response in bold)

Thank you for this interesting paper. Were you able to code/ adjust for women who had had a previous Unilateral S/O and then underwent a hysterectomy and Unilateral Salpingectomy? Not sure if these were a significant number of the 61000 who didn't have surgery of interest.

**Unfortunately, not because we only had data from 2011 to 2016, we could not have accurately captured people who had two unilateral salpingectomies over two separate surgeries. Because OS is defined as bilateral salpingectomy, we have excluded the people who had unilateral salpingectomies from this analysis. These**

**unilateral salpingectomies are likely occurring for very different clinical indications, and because we already had so many groups to consider, we felt the cleanest way to present these data was to exclude them.**

**Reviewer 3:** Dr. Malou E. Gelderblom  
General comments (author response in bold)

#### Introduction

The introduction is easy and well-written. However, argumentation seems missing about why insights in the uptake of the opportunistic salpingectomy is relevant.

**We have added the following to the introduction section “We hypothesized that rates increased across all included jurisdictions in Canada following 2011, and it is important to understand how commonly OS is performed, as it is an important method of primary prevention for ovarian cancer.(26)” Page 25**

Page 4 line 24 please add reference: Tubal ligation and risk of ovarian cancer. Piek JM, van Diest PJ, Zweemer RP, Kenemans P, Verheijen RH. Lancet. 2001 Sep 8;358(9284):844

**We have added the reference. Page 4**

Page 4 – line 26 : I would recommend defining BC prior to abbreviating it. Subsequently, this abbreviation is not consequently used throughout the manuscript.

**We have defined BC at its first use in the manuscript and are consistently abbreviating throughout the manuscript.**

Page 4 – line 49 – page 5 – line 1: I would suggest to change ‘there are no indicators’ in ‘there seems to be no indicators’ as it lacks actual prospective data on the effect of OS on onset of menopause and the Cochrane review of van Lieshout & Steenbeek [1] show a potential reduction in AMH by OS (however not significant) possibly indicating a minor decline in ovarian reserve.

**We have rephrased this and it now reads “Finally, there seem to be no indicators of an earlier age of onset of menopause following OS.(20-24)” Page 5**

Page 5 - line 1: The comma after the word ‘mortality’ should be replaced by a period ‘.’.  
b

Page 5 – line 17: What is the reason that you only looked to the uptake until 2016, and not till present day?

**These were the most recent data available at the time the request was made. We have added some discussion to the limitations section around this. It now reads “First, we are limited by the fact that our data extend only until 2016. Given that there was a trend of increasing uptake across many jurisdictions, it is likely that rates of OS are currently higher in many, and possibly all, jurisdictions studied. However, given the change between 2011 and 2016, and the fact that these data include two full calendar years following the SOGC recommendation for OS, we expect the trends reported are still relevant.” Page 12**

#### Results

The results section includes clear figures that give visual insights into the data at glance.

Page 6 – line 33 to 38: The time period of data collection is mentioned twice. Moreover, you have mentioned the study period April 1st until March 31st 2017, in contrary to the

study period of 2011 until 2016 mentioned in both the introduction and method. Could this contrast be explained by the fact that it concerns fiscal years? If so, please clarify this in your methods.

**Thank-you for pointing this out. We agree that this was confusing and have clarified in the methods section. It now reads “We included all people who had undergone any, or any combination, of hysterectomy, salpingectomy, oophorectomy and tubal ligation between April 1st, 2011 and March 31st, 2017 (referred to hereafter as 2011 to 2016 as these are the relevant fiscal years).” We have removed the dates from the results section. Page 6**

Page 6 – line 45: Why did you exclude surgeries concerning hysterectomies with unilateral salpingectomy? Could an opportunistic salpingectomy not also be discussed with these women? Now, one of the fallopian tubes remains in place, while this (one) fallopian tube could have been opportunistically removed. In my opinion, these group of women should be included in the proportion of women who did not undergo an opportunistic salpingectomy.

**We had considerable discussion around this issue and felt that because we could not be certain of the presence or absence of the other ovary and fallopian tube (given that we only had 6 years of data), it was cleanest to exclude these. When working in BC data, we usually do as you suggest and include them the group not undergoing OS, but we also have access to more historical data when we are working with our provincial data and so can look back in time for any indication that the other fallopian tube had previously been removed.**

#### Discussion

It would be pertinent to include some other limitations of the study in the discussion. For example, according to these data it is not known whether the bilateral salpingectomy was actually performed as opportunistic or whether there was another indication. This can give an overestimation of uptake.

**We have added the following to the limitations section “Second, like all studies relying on administrative data, there is a risk of imprecision given our dependence on database accuracy of coding. This includes the fact that we cannot be certain that all bilateral salpingectomies performed at the time of hysterectomy or for tubal sterilization were done for the purpose of primary ovarian cancer prevention (i.e., they may not all have been OS). However, given how rare bilateral salpingectomy was prior to recommendations being made in 2010,(17) and that there is no reason to believe that the few indications for bilateral salpingectomy are increasing over time, we are confident that most practice change is driven by uptake of OS.”**

In addition, discuss why such large proportion of young women underwent BSO (Figure 3a). Moreover, this data does not provide insight in whether the option of opportunistic salpingectomy was discussed with the patient. According to Gelderblom & van Lieshout et al.[2], some of the women who are offered opportunistic salpingectomy, chose against it.

**With respect to the young people undergoing hysterectomy with BSO, we have added a supplemental table that outlines the diagnostic codes associated with these surgeries. It reveals that most young people having this surgery are receiving gender affirming care. We have added the following sentence to the results. “Supplemental table 2 explains the high share of 15–24-year-olds who had hysterectomy with BSO as mostly being gender affirmation surgeries.” Page 9**

**We have clarified this in the limitations section, which now reads “We are also only able to analyze uptake of OS using surgeries performed, and are thus unable to determine when OS was discussed with a patient and the patient declined, which research has suggested could be a source of differences in uptake.(49)” and cites the Gelderblom study (which was not available at the time of submission of this article). Page 13**

Page 9 – line 31 – Who do you mean with people, patients or physicians?  
**We mean patients and have edited it to say patients.**

Page 10 line 47: please add this reference and elaborate on the possibility with this data in hand: Patients' and professionals' perspectives on implementation of opportunistic salpingectomy: a mixed-method study. Gelderblom ME, Van Lieshout LAM, Piek JMJ, De Hullu JA, Hermens RPMG. BMC Health Serv Res. 2021 Jul 25;21(1):736 [2]  
**We have added discussion of this article and its finding to our limitations section. It now reads “Third, we are also only able to analyze uptake of OS using surgeries performed, and are unable to determine when OS was discussed with a patient and the patient declined, which research has suggested could be a source of differences in uptake.(49)” Page 13**

Page 11- line 45: please add the Cochrane review on this topic and elaborate on the chance that a person does get into menopause prematurely (see data on AMH): Hysterectomy with opportunistic salpingectomy versus hysterectomy alone. van Lieshout LAM, Steenbeek MP, De Hullu JA, Vos MC, Houterman S, Wilkinson J, Piek JM. Cochrane Database Syst Rev. 2019 Aug 28;8(8)  
**We have added discussion of this to the section that previously discussed ovarian function and an earlier onset of menopause. This section now ends with “There is still some uncertainty around ovarian function following OS. A recent Cochrane systematic review reported finding no evidence of any difference in onset of menopause after hysterectomy with salpingectomy but using the ranges of anti-mullerian hormone concentrations reported across studies, onset of menopause could occur somewhere between 0 and 20 months earlier in the hysterectomy with salpingectomy group.(42)” Page 12**

Page 11 line 12: please add: Ovarian cancer risk after salpingectomy for ectopic pregnancy or hydrosalpinx: results of the OCASE nationwide population-based database study. van Lieshout LAM, Piek JMJ, Verwijmeren K, Houterman S, Siebers AG, de Hullu JA, Bekkers RLM. Hum Reprod. 2021 Jan 1;36(1):211-218  
**We have added the reference. While it reports null findings, we think it still suggests a protective effect for salpingectomy that will increased with increasing followup, and thus have cited it following the statement “Although a large prospective observational study of the effectiveness of opportunistic salpingectomy for cancer prevention is urgently needed, historical studies lead us to hypothesize that OS will be effective in preventing high grade serous ovarian cancer.(43-47)” Page 12**

**Reviewer 4:** Dr. Joanne Kotsopoulos  
**Institution:** Women's College Research Institute  
General comments (author response in bold)

Thank you for the opportunity to review this timely analysis of opportunistic salpingectomy (OS) in Canada. The authors present the existing data by region, rurality and age, and also provide a few suggestions for the observed discrepancies by geography. Although the topic is of interest and the data are robust, there are few missed opportunities to provide more insight into the observations, as well as a little more discussion on their hypotheses. Overall, this is an important study and contributes to the emerging knowledge in the field of the fallopian tubes as a source of serious cancers in women and the potential for OS to prevent a subset of the cases, and hopefully, impact mortality rates.

1. The authors make the statement that ovarian cancers often, mostly, etc. originate in the fallopian; however, this should not be such a definitive assumption. The data, to my knowledge, suggests that a subset (whether more or less than half is not clear), actually originate in the tubes.

**In the introduction section we have stated: “The recent understanding that the most common and lethal form of ovarian cancer, high-grade serous (HGSC) often originates in the fallopian tube, has introduced a prevention opportunity. (8-12)” We think the body of evidence supports this statement. Even if the proportion is as low as 50% (and the available evidence does not support the proportion being this low), we think it still makes sense to use the term often. Page 4**

2. The impact of OS on menopause is not entirely clear. While there are some data that exist, one cannot definitively say that tubal removal does not impact onset of menopause or related symptoms. Perhaps this can be better clarified.

**We have added a more nuanced discussion of this literature to the discussion section. Please see our response to reviewer three’s suggestion above for more detail. We have also edited the introduction. It now reads “Finally, there seem to be no indicators of an earlier age of onset of menopause following OS, although some uncertainty remains regarding ovarian function following OS. (20-24)” Page 5**

2. The exclusion of Quebec is not clear. Perhaps this can be better described. **While we would have loved to include Quebec, Quebec data are not included in the database we used. We have added the following section to the methods section:**

**“Study design This was a large retrospective descriptive analysis of all Canadian jurisdictions except Quebec, as Quebec data are not recorded in the database used in this study.” Page 5**

3. The methods section requires a flow chart and definitely more information on the total numbers that were excluded based on the various exclusions that were provided. Furthermore, there needs to be a Table 1 in the results section which shows the characteristics of the women included in they analysis stratified by type of cancer, province/territory, etc. to provide the reader with some basic information about the population of women included in the analysis. Furthermore, why is there no discussion on potential indications for salpingectomy vs. hysterectomy etc as it is well-established that certain conditions would require one surgery vs. the other. Also, there seems to be no discussion on uni vs. bilateral surgery.

**We have added quite a bit to the methods section. We agree that there was an important lack of clarity around the unilateral surgeries that we have now clarified. The new study participants section reads:**

**“Study participants We included all people who had undergone any, or any combination, of hysterectomy, salpingectomy, oophorectomy and tubal ligation between April 1st, 2011 and March 31st, 2017 (referred to hereafter as 2011 to 2016 as these are the relevant fiscal years). These were the most recent data available at the time of the data request. We excluded people who were less than 15 years old at the time of surgery, as these gynecologic surgeries are rare among people younger than 15 and thus may be more likely to represent data errors. We excluded anyone whose records included a diagnostic code for ovarian, uterine, cervical, or fallopian tube cancer (International Classification of Diseases code 10-CM ICD-CM C53-C57), and anyone who underwent a unilateral salpingectomy, as opportunistic salpingectomy refers to the removal of both fallopian tubes as primary prevention of ovarian cancer.” Page 6**

**We have also included a Table 1 in the results section, and discuss the differences in the study population. It reads “Table 1 illustrates that more OS occurred toward the end of the study period, that there was higher rates of OS in urban areas, and that the diagnostic codes associated with the surgery were quite similar across the groups.” Page 8**

4. I think it is important that the authors discuss the importance of OS for permanent sterilization rather than a cancer prevention option per se. Elaborating on this, is that there should be some discussion on tubal ligation vs. OS with respect to safety, timing, etc. especially if this is why clinicians are still opting for ligation instead of OS.

**We have added the following to the discussion section “Research has been published illustrating no increased perioperative or postoperative complications when comparing OS for sterilization to tubal ligation.(17, 19). Salpingectomy has also long been considered the preferred method to ensure definitive sterilization when tubal ligation fails.(31)” Page 11**

5. Given Ontario is a large province (population size), it seems to be left out of the discussion.

**This is not a reflection of not considering Ontario important but rather a reflection of it’s status as middle of the pack in terms of uptake of OS. Given that the word limit is very tight, we cannot discuss all the provinces, and thus chose to focus on the extremes. To discuss Ontario and not any of the other provinces that are middle of the pack seemed problematic, so we have chosen to continue to focus on the extremes.**

6. Although OS does have an important role in preventing a subset of cases, the assumption that it would prevent all cases is a bit overstated. The manuscript would benefit from a more thoughtful discussion of the existing literature including the pathologic, clinical and observational data supporting the topic.

**We have changed the language to be more conservative. The statement remains true even in a scenario where you estimate that OS is only 40% effective in preventing ovarian cancer. It reads “The data presented herein show that we missed ~180,000 opportunities to prevent an ovarian cancer in the included Canadian jurisdictions between 2011 and 2016. At a lifetime risk of ovarian cancer of 1.4%, this could translate into thousands of ovarian cancers that could have been prevented.” Page 13**

**We are happy to revise to include more discussion of the historical data on salpingectomy, but are concerned about the word limit of the paper.**

8. The discussion also requires more reflection on the age-specific data. This seems to be ignored in its entirety. Why would one not provide a BSO if the woman is already menopausal and undergoing a hysterectomy? Etc.

**We have added the following to the discussion section: “As expected, rates of hysterectomies with bilateral salpingo-oophorectomy did not change over the study period, as these surgeries were not targeted by any of the opportunistic salpingectomy practice recommendations and tend to occur for other indications. This surgery is often provided with ovarian cancer prevention in mind to older women who are already menopausal, and it was consistently the most common form of hysterectomy among those older than 65 across our study period.” Page 10.**

**While we recognize that this is not likely the fulsome discussion you were looking for, we are severely constrained by the word limit, but do agree that the point should be made that this is an appropriate surgical choice in older women.**

Minor:

1. Some spelling mistakes on line 43-44 page 9 of discussion.

**Thank-you. These have been corrected.**