

Opportunistic Salpingectomy: A New Scope of Preventing a Deadly Disease

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Abstract

Background: Symptoms of ovarian cancer are non-specific and often do not arise until the cancer is in a late stage. Such late onset of symptoms and the lack of an effective screening test result in diagnosis at an advanced-stage for most patients of ovarian cancer. The fimbrial end of the fallopian tube has recently been suggested as the site of origin for epithelial ovarian cancers (EOC). Therefore, a change in practice with opportunistic salpingectomy (OS) at the time of hysterectomy has been advocated for prevention of ovarian cancer. Different gynaecological societies have published statements in favour of opportunistic salpingectomy in women at average population risk for ovarian cancer prevention. In recent years, salpingectomy has been increasingly performed for tubal sterilization also. We have gone through the available scientific publications and international guidelines in preparing this brief review in an attempt to be familiar with the recent updated views regarding this issue.

Keywords: Opportunistic salpingectomy; Prevention of ovarian cancer.

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Introduction

Ovarian cancer ranks fifth in cancer deaths among women and is the commonest cause of death from cancer of the female reproductive system. A woman's risk of getting ovarian cancer during her lifetime is about 1 in 78 and her lifetime chance of dying from ovarian cancer is about 1 in 108.¹ Ferlay et al. reported that in 2018 there were 295,400 newly diagnosed ovarian cancer cases and 184,800 deaths due to ovarian cancer worldwide.² The American Cancer Society estimates that in the United States about 19,880 women will be newly diagnosed with ovarian cancer and about 12,810 women will die from the disease in 2022.¹ The main risk factors for developing ovarian cancer are advancing age and

family history. Approximately 10-25% of ovarian cancers are associated with an identified hereditary genetic abnormality.⁴⁻⁸ Women with BRCA1 and BRCA2 mutation are at higher-risk of developing the disease than general population with an average cumulative risk of between 40-75% and 8-34%, respectively.⁹⁻¹¹ The carcinomas that develop in patients with hereditary BRCA1 or BRCA2 mutation are commonly high-grade serous in type.¹²

Symptoms of ovarian cancer are non-specific and often do not arise until the cancer is in a late stage. Such late onset of symptoms and the lack of an effective screening test result in diagnosis at an

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advanced-stage for most patients of ovarian cancer.¹³⁻¹⁵ Ovarian cancer screening is not recommended for women at average risk because the combination of low test specificity and low prevalence results in an unacceptably low positive predictive value. Even for women at increased risk, screening has not been proven to be an effective tool in lowering ovarian cancer mortality even with strict adherence to screening protocols.¹⁵⁻¹⁹ The combined evidence from three large clinical trials does not support a reduction in mortality associated with annual cancer antigen 125 (CA125) and/or ultrasound imaging among women in the general population. However, there are effective strategies to decrease risk, and prevention remains an essential strategy to reduce deaths from ovarian cancer.²⁰ So the prevention of ovarian cancer has become an important aspect in attempts to decrease its incidence. For those at high risk of developing ovarian cancer, with or without genetic mutations and/or family history, studies have shown that risk-reducing bilateral salpingo-oophorectomy upon completion of child-bearing should be the standard of care.²¹ Bilateral salpingo-oophorectomy has traditionally been offered for many years at the time of hysterectomy for nonmalignant disease to prevent ovarian cancer later in life.²² However, in young premenopausal women with no genetic or family history affecting their baseline risk of ovarian cancer, the risks of early age oophorectomy greatly outweighs the benefits and this procedure is now being increasingly avoided due to the well recognized adverse effects from the loss of ovarian hormone production.^{21,23}

Recent evidence has indicated that epithelial ovarian cancer, which is the most common and lethal form of ovarian cancer, originates in the distal fallopian tube and recommendations for surgical removal of the fallopian tube i.e. bilateral salpingectomy at the time of other gynaecologic surgeries particularly hysterectomy and tubal sterilization have been made.²⁴ Removal of the fallopian tubes for the primary prevention of ovarian cancer in a woman already undergoing

pelvic surgery for another indication is termed as opportunistic salpingectomy. Opportunistic salpingectomy at the time of hysterectomy or as an alternative to bilateral tubal ligation may reduce the incidence of ovarian cancer significantly in the patients at average population risk of having ovarian cancer. However, it does not eliminate the risk of ovarian cancer entirely.²⁵

Committee of American College of Obstetricians and Gynecologists (ACOG) recommends that, counseling should be done with the women who are undergoing routine pelvic surgery about the risks and benefits of salpingectomy including an informed consent discussion about the role of oophorectomy and bilateral salpingo-oophorectomy in prevention of ovarian cancer with their pros and cons. The risks and benefits of salpingectomy should also be discussed with patients who desire permanent sterilization. Salpingectomy at the time of hysterectomy or as a means of tubal sterilization appears to be safe and does not increase the risk of complications such as blood transfusions, readmissions, postoperative complications, infections, or fever compared with hysterectomy alone or tubal ligation. Additionally, ovarian function does not appear to be affected by salpingectomy at the time of hysterectomy based on surrogate serum markers or response to in vitro fertilization. On the other hand, bilateral salpingo-oophorectomy causes abrupt surgical menopause and may increase the risk of cardiovascular disease, cancer other than ovarian cancer, osteoporosis, cognitive impairment, and all-cause mortality. Furthermore, prophylactic oophorectomy practiced so far did not improve survival at any age.^{18,25-27} A number of observational studies have shown that bilateral salpingo-oophorectomy before age 45 or 50 years is associated with increased all-cause mortality despite reduced rates of ovarian cancer.²⁸⁻³² The strategy of bilateral salpingo-oophorectomy reduced the mortality rate from ovarian cancer in the Nurses' Health Study by 94%; however, the overall risk of death from any cause following bilateral salpingo-oophorectomy increased by 12%, reflecting the protective effect of

estrogen in preventing cardiovascular disease before age 50.¹⁹ Therefore, current guidelines advise against bilateral salpingo-oophorectomy in premenopausal women.³³⁻³⁵ Rather Society of Gynecologic Oncology (SGO), American College of Obstetricians and Gynecologists (ACOG) and many other concerned bodies are now advocating that salpingectomy during hysterectomy or during Cesarean section is an appropriate option for risk reduction of ovarian cancer.^{25,36} It is also an approach that should be offered to patients undergoing other pelvic surgeries, including myomectomy and treatment of endometriosis, in whom fertility is no longer desired or fallopian tubes are damaged.^{37,38}

Tubal origin of epithelial ovarian cancer

Ovarian cancer is a heterogeneous disease and its cellular origins remain an area of active debate.^{39,40} It has been postulated that ovarian cancers can arise from the ovarian surface epithelium, fallopian tube epithelium and ectopic endometrium and different histological subtypes have different origins.^{41,42} Epithelial ovarian cancers (EOCs) comprise a heterogeneous group of neoplasms including the pathological subtypes serous (68%), clear cell (13%), endometrioid (9%) and mucinous (3%).^{43,44} Serous ovarian carcinomas are further divided into low-grade (type I) and high-grade (type II) serous ovarian carcinomas (LGSC and HGSC respectively) with individual distinct clinical characteristics and genetic origin and HGSC differs from LGSC at molecular level.^{41,45} Two-thirds cases of LGSC are associated with KRAS or BRAF mutations and some have HER2 (ERBB2) mutations, but there is no association with p53 mutations. In contrast, HGSC has an extremely high rate of p53 mutations (approaching 100%), somatic BRCA mutations and an absence of KRAS, BRAF or HER2 mutations.^{7,45,46} HGSC is therefore characterized by p53 mutation as well as dysfunction in BRCA1 and BRCA2.⁴⁶

High-grade serous carcinomas (HGSC) are among the most lethal ovarian malignancies and account

for approximately two-thirds of all invasive ovarian cancers. It is usually diagnosed at an advanced stage, and are largely responsible for the poor outcomes associated with this disease as most women with HGSC ultimately relapse, develop resistance to chemotherapeutic agents and succumb to their disease.^{47,48}

The discovery of BRCA1 and BRCA2 susceptibility genes in the mid-1990s and recent improvements in pathologic assessment the fallopian tube have demonstrated that a majority of HGSCs arise in the fallopian tube in the form of serous tubal intraepithelial carcinomas (STICs) and they later spread to the ovary and/or the peritoneum.⁴⁹⁻⁵⁴ Consequently, in 2014, the International Federation of Gynecology and Obstetrics (FIGO) staging system for high-grade serous cancers was modified to classify the primary site of disease collectively as ovarian, fallopian tube and primary peritoneal.⁵⁵

The involvement of fallopian tube in ovarian cancer was first suggested as early as 1896, with the case report of a primary fallopian tube cancer with pathological characteristics very similar to ovarian cancer.⁵⁶ There has been a rapidly increasing body of evidence supporting the fallopian tube as the site of origin of HGSC over the past few years. Crum et al.⁵⁷ commented in a review article that the association between the fallopian tube and HGSC as 'indisputable'. Closer histological examination of the fallopian tubes in high-risk women and women with sporadic HGSC has also led to the discovery of potential precursor lesions for high-grade pelvic serous cancers.⁵³ More recently, examination of the fallopian tubes removed at risk-reducing bilateral salpingo-oophorectomy (RRBSO) from women with BRCA1 and BRCA2 mutations revealed the presence of occult cancers in the fimbriae of fallopian tubes in 5-15% of these high-risk women and serous tubal intraepithelial cancers (STICs), which are preinvasive lesions, in the fimbriae in 1-6% of the women.⁵⁸⁻⁶⁴ With emphasis, the precursor lesions have never been found in the ovarian epithelium.⁶⁵

Such finding of serous tubal intraepithelial carcinoma (STIC) in specimens from risk-reducing salpingo-oophorectomy and the presence of synchronous STIC lesions in patients with HGSC of the ovary and peritoneum, resulted in development of a consensus statement in 2016 and detailed histopathological assessment of the fallopian tube fimbriae in cases of ovarian/tubal/peritoneal carcinoma using the Sectioning and Extensive Examination of the Fimbrial end (SEE-FIM) protocol was recommended.⁶⁶⁻⁶⁹ This was to improve accuracy and consistency in primary site assignment, as fallopian tubes appear macroscopically normal even in the presence of these lesions.^{66,67} Detailed and extensive examination of the distal fallopian tube using this protocol has revealed tubal involvement in up to 70% of women diagnosed with ovarian or primary peritoneal HGSC irrespective of their BRCA 1 or 2 mutation status, including the presence of fimbrial STICs in 40-60% of these women.^{39,50,70-74} The proportion of fimbrial STICs increased with more complete examination of the fallopian tube.^{70,75} Another interesting and important finding is that STICs were not observed in women with non-gynaecologic or benign conditions.⁷⁸ Based upon these findings, it has been proposed that tubal neoplasia is the primary lesion in HGSC and that these lesions spread to the ovary and peritoneum.^{39,70} It has also been clearly evidenced that early-stage HGSCs almost always arise from the fallopian tube, whereas in advanced-stage disease, only 10-60% of cases are associated with a concurrent STIC lesion.^{39,77}

The theory that STICs are the precursor lesion to HGSC is further supported by the finding of identical TP53 mutations in STICs and concomitant ovarian and/or peritoneal cancers.^{50,78} Essentially 100% of de novo HGSCs contain TP53 alterations. Recent evidence suggests that cells from non-malignant early serous proliferations (ESPs) shed from the tube undergo subsequent malignant transformation and results in sudden widespread peritoneal disease.⁷⁹ Molecular markers and gene expression

profiles of HGSCs demonstrate lineage continuity of specific TP53 mutations between early serous proliferations (ESPs) and concurrent serous carcinomas, further supporting this theory. This dualistic 'tubal hypothesis' has become the most supported theory for the pathogenesis of EOC and provides an explanation for early peritoneal dissemination and the elusiveness of early detection which are the hallmarks of the disease.⁷⁹

It has also been suggested that STICs in the fallopian tube are preceded by earlier fallopian tube lesions. One of such precursors is the 'p53 signature', which is a focus of 12 or more cells with normal morphology, primarily localized at the fimbriated end of the fallopian tube, but with strong p53 immunostaining. Over 90% of STICs have p53 signatures; p53 signatures have been reported in direct association or contiguous with STICs, and p53 signatures share identical TP53 mutations with both STICs and invasive cancers. All of these facts strongly suggest a clonal relationship among these tissues.^{53,78,80} Identical p53 mutations in p53 signatures in both STICs and invasive cancers suggest that these represent an early event in the pathogenesis of HGSC. Adult epithelial stem cells undergo cell repair through mechanisms including clonal growth and self-renewal. These processes make the cells susceptible to DNA damage and subsequent malignant change. The distal fallopian tube has been shown to contain double the amount of stem-like epithelial cells compared to the proximal end and therefore may play a role in initiating neoplastic transformation, even in the presence of BRCA1/BRCA2 DNA repair proteins.^{81,82} Exposure of the distal fallopian tube to locally elevated levels of inflammatory cytokines could contribute to the development of precursor lesions and eventual malignant transformation of these cells.^{83,84} In addition, gene expression of high-grade serous carcinomas is more closely related to the fallopian tube morphology than to the ovarian surface epithelium as high-grade serous carcinomas express a müllerian marker (PAX8) but not a mesothelial marker (calretinin).²⁵

Two distinct pathways in ‘ovarian cancer’ carcinogenesis have been proposed. The first involves the incorporation of müllerian epithelium into the ovary, derived from the fallopian tube through exfoliation of tubal cells or tubal ovarian adhesions, or may be secondary to müllerian metaplasia of ovarian surface epithelium. This may lead to formation of endosalpingiosis, cortical inclusions or endometriosis. This incorporated müllerian epithelium may even give rise to benign and borderline serous tumours, low-grade serous adenocarcinomas, endometrioid or clear cell tumours but rarely HGSC. The second pathway involves malignant transformation of the distal fallopian tube mucosa through p53 signatures and the development of STIC. These STIC lesions may invade locally into the underlying tubal wall; exfoliate onto the surface of the ovary or into the peritoneal cavity, or a combination of these possibilities. This exfoliation into the peritoneal cavity could explain the clinical finding of widespread peritoneal HGSC in the absence of a significant volume of invasive disease in the fallopian tube or ovary.^{50,85}

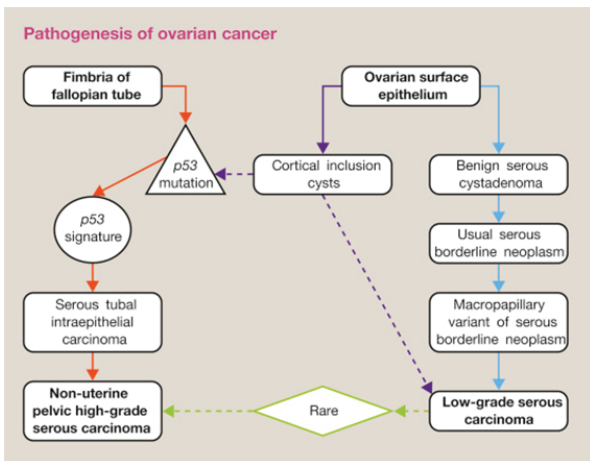


Fig. 1: Pathogenesis of HGSC⁸⁵

Whether the fallopian tube is the source of all high-grade serous tumours with or without a genetic predisposition is debatable. Because a STIC or other precursor lesion is not identified in the fallopian tubes of all women with high-grade tumours and rates of STICs in both sporadic and hereditary cases vary substantially.^{77,86} It is not clear if STICs are causally associated with the

subsequent risk of developing invasive cancer, although an increased risk of high-grade serous peritoneal carcinoma following a diagnosis of a STIC has been observed in some (but not all) women.

Recommendations for opportunistic salpingectomy

As researchers are increasingly giving emphasis on the role of the fallopian tube in ovarian cancer, and the risk reducing bilateral salpingo-oophorectomy (RRBSO) is inappropriate for prevention in the general population, recommendations have been made regarding the treatment of the fallopian tube in common gynaecologic surgeries by several associations and experts over the recent years (Table I).

Table I: Statements of gynaecological societies on opportunistic salpingectomy

Year	Associations or Experts	Recommendation
2010	Ovarian Cancer Research Team(OVCARE) ³⁶	In women with average risk, consider surgical removal of fallopian tubes at the time of hysterectomy. Replace tubal ligation with excision bilateral salpingectomy for the purpose of permanent contraception.
2011	Society of Gynecologic Oncology of Canada ³⁶	Officially endorsed the cancer prevention strategy and added that physicians discuss the risks and benefits of bilateral salpingectomy with patients undergoing hysterectomy or requesting permanent irreversible contraception
2011	Royal Australian and New Zealand College of Obstetricians and Gynecologists ³⁷	Doctors should discuss the risks and benefits of bilateral salpingectomy with patients undergoing by hysterectomy for benign disease
2013	Society of Gynecologic Oncology (SGO) ³⁶	For women at average risk of ovarian cancer, risk-reducing salpingectomy should also be discussed and considered with patients at the time of abdominal or pelvic surgery, hysterectomy or in lieu of tubal ligation
2014	Royal college of Obstetricians and Gynecologist ⁸⁵	Women who are not at high risk for BRCA mutation and have completed their families should be carefully considered for prophylactic removal of the fallopian tubes with conservation of ovaries at the time of gynecological or other intraperitoneal surgery
2015	American College of Obstetricians and Gynecologists (ACOG) ⁸⁸	Women at population-level risk of ovarian cancer who are undergoing ovary-sparing hysterectomy for benign indications should be offered bilateral salpingectomy to reduce their risk of ovarian cancer. Clinicians can communicate that bilateral salpingectomy can be considered a method that provides effective contraception
2015	Commission Ovary of the AGO ⁸⁹	During preoperative counseling prior to hysterectomy, all patients should be informed about the potential beneficial impact of opportunistic salpingectomy and the associated risks

Opportunistic salpingectomy in average-risk women

The emerging evidence of the tubal origin of EOC has led to support for opportunistic bilateral salpingectomy (OS) in the general population. The most recent, largest and most rigorous study of the relationship between ovarian cancer and bilateral salpingectomy to date was a population-based retrospective Swedish study using health registers incorporating more than 5.5 million women and 30,000 ovarian cancer cases. They reported that

women who had undergone salpingectomy during hysterectomy for benign disease had a decrease in subsequent risk for ovarian cancer with a hazard ratio of 0.65 and that women undergoing bilateral salpingectomy had 50% lower risk than those undergoing unilateral salpingectomy.⁹⁰ Other observational studies have shown similar results. Danish researchers used a national database to study the relationship between bilateral salpingectomy and ovarian cancer in a retrospective cohort study and they reported that bilateral salpingectomy reduced the risk for ovarian cancer by 42%.⁹¹ According to a recent meta-analysis, opportunistic salpingectomy might decrease the overall incidence of ovarian cancer up to 50%.⁹² Some researchers suggest a risk reduction up to 70%, based on the assumption that OS will prevent all ovarian cancers of the serous subtype (HGSC).⁹³ A statistical model predicted that the widespread adoption of OS at the time of surgery for benign gynaecologic indications would decrease the incidence of HGSC by 40% over the next 20 years.⁹⁴ Recent studies have shown that prophylactic salpingectomy was helpful not only in preventing high-grade serous type ovarian cancer, but also in decreasing other adnexal pathologies.²⁷

The association between bilateral tubal ligation (BTL) and a decreased risk of ovarian cancer is well established, resulting in an overall 20-40% lower rate of EOC in women after BTL.⁹⁵⁻⁹⁹ The impact of BTL appears to be greatest on endometriosis-associated histologies such as clear cell and endometrioid carcinoma; this may shed light on the mechanism of protection.^{91,100} However, data suggests that excisional tubal sterilization may confer a greater degree of protection than tubal ligation. A population-based, nested case-control study by researchers from the Rochester epidemiology project published in 2014 concluded that the adjusted risk of EOC was decreased by 64% after excisional tubal sterilization methods compared to those with non-excisional methods of sterilization.¹⁰¹ Tubal ligation (TL) is also known to reduce the risk of EOC by 20-40% especially in endometrioid

carcinoma (EC) by 52% and clear cell carcinoma (CCC) by 48%, supporting the theory that these cancers may have a more proximal tubal or endometrial origin than HGSC, as the distal tube remains in situ after TL where STIC lesions are found.^{97,102,103} However, tubal ligation reduces the risk of developing high-grade serous cancers by only 19%, supporting the theory that these cancers arise within the distal end of the remaining fallopian tube.¹⁹ Whereas, Sterilization with removal of the fimbrial end of the tube has been shown to be more effective at risk reduction of EOCs than TL.^{67,100.}

Cost-effectiveness

Implications of widespread performance of opportunistic salpingectomy (OS) on health care system costs warrant further study and concerns have been raised. Evidence till date indicates a favorable cost-benefit ratio for OS. Kwon et al.¹⁰⁴ have used a decision analytic model to estimate the cost-effectiveness of OS as an ovarian cancer prevention strategy for the general population. Using the assumptions that OS, BSO, hysterectomy, and tubal ligation each confer a 50%, 90%, 20%, and 30% reduction in risk for ovarian cancer, OS was found to be cost-effective. The model reported that hysterectomy with OS was less costly than hysterectomy alone or with bilateralsalpingo-oophorectomy (BSO) but more effective with average comparative life expectancy gains of 1 week and 2 months respectively. For sterilization, OS was more costly than tubal ligation but more effective with an average life expectancy gain of 1 week. Bilateral salpingo-oophorectomy would lead to an 88% reduction in ovarian cancer but also an additional 934 deaths from premature menopause without routine use of HRT.¹⁰⁴

In a cost-effective analysis by Naumann et al.¹⁰⁵, it was estimated that universal opportunistic salpingectomy may prevent 1854 deaths per year from ovarian cancer and may reduce healthcare costs. Similar comment was observed in the population-based retrospective cohort study by McAlpine et al.¹⁰⁶

A decision-analytic and cost-effectiveness study on 110,000 pregnant women undergoing Cesarean delivery who desired permanent sterilization in the US population compared 3 strategies: (1) bilateral tubal ligation, (2) bilateral opportunistic salpingectomy, and (3) postpartum long-acting reversible contraception. Bilateral tubal ligation and bilateral opportunistic salpingectomy with Cesarean delivery were both cost-effective strategies for permanent sterilization and ovarian cancer risk reduction.¹⁰⁷ Similar observation was shown in a cost effectiveness analysis study by Dilley et al.¹⁰⁸ In their model, salpingectomy was cost-effective with both procedures, but the advantage was greater at time of hysterectomy.

Impact on ovarian function

A concern with OS is its potential detrimental effect on ovarian blood supply, and therefore, impact on ovarian function and onset of menopause. Evidence suggests that women with a prior hysterectomy experience menopause earlier than those without hysterectomy, raising concerns about the additional impact of salpingectomy on ovarian perfusion.^{109,110} Salpingectomy, when performed correctly, should not impact the ovarian blood supply and, therefore, should not have an impact on ovarian hormone production, ovulation or age of menopause.¹⁴

In a multicenter trial by Song et al.,¹¹¹ 68 patients undergoing laparoscopic hysterectomy for benign indications were randomized to OS versus no salpingectomy. Although AMH levels were significantly decreased from preoperative levels in both groups, there was no significant difference between the OS and no-salpingectomy groups. A similar finding was observed in a study by Morelli et al.,¹¹² which demonstrated similar levels of AMH, follicle-stimulating hormone, and estradiol in patients who underwent hysterectomy with or without OS, and there were no differences in ovarian function between the groups postoperatively. A similar study by Findley et al. compared 30 premenopausal women undergoing laparoscopic hysterectomy with ovarian preservation with and without opportunistic

salpingectomy for benign indications. Antimüllerian hormone (AMH) levels were not significantly different at baseline, 4-6 weeks after surgery, and 3 months postoperatively in both groups. No differences in operative time or estimated blood loss were found.¹¹³ Data from a randomized controlled trial also suggests that even when a wide excision is taken to excise all fallopian tube tissue, salpingectomy does not negatively impact ovarian reserve or perioperative morbidity.¹¹⁴

Another study also concluded that there was no indication of an earlier age of onset of menopause among the population of women who underwent hysterectomy with opportunistic salpingectomy and opportunistic salpingectomy for sterilization as measured by physician visits for menopause and initiation of hormone replacement therapy.¹¹⁵ A larger randomized controlled trial revealed that 3 months post-surgery the AMH levels in both groups were significantly lower than the preoperative AMH levels.¹¹⁶ There were however no significant differences between the both groups. In a larger multicentre randomized controlled trial there was no difference in AMH levels before surgery and 6 months after surgery.¹¹⁷ These two studies showed that on the short term (3 to 6 months postoperative) at least there is no negative effect of OS on the ovarian function after hysterectomy. In one observational study, ovarian function was monitored in 71 women undergoing laparoscopic hysterectomy with opportunistic bilateral salpingectomy for 3-5 years after surgery. In these women, follicle-stimulating hormone, antimüllerian hormone (AMH), antral follicle count, vascular index, flow index and vascular flow index were used to determine ovarian function and then compared with a control group that included 652 healthy women with intact uterus and adnexa. Results showed no difference between the two groups reassuring that ovarian function can be safely preserved with opportunistic bilateral salpingectomy.¹¹⁸

In a retrospective observational cohort study, the impact on menopausal symptoms one year after

hysterectomy with or without OS was assessed. Data of menopausal symptoms like hot flushes, sweats or palpitations of 4906 women were analyzed and it showed a significant increase in menopausal symptoms in the group who had a hysterectomy with OS. However, in the age-stratified adjusted analysis, only women at the age of 44-69 years remained at significant risk of menopausal symptoms one year after OS.¹¹⁹

However, long-term effects in detail have not been analyzed systematically after hysterectomy with OS or OS for sterilization. While laboratory measurements such as AMH provide reproducible, objective data, further investigation is warranted using more clinically relevant endpoints such as the timing and severity of menopausal symptoms.¹⁰⁰ This requires further study, because, if OS results in early menopause, the ovarian cancer mortality benefit may be entirely offset by the increase in all-cause mortality. While the short-term data indicating hormonal equivalence between the OS and hysterectomy alone is somewhat reassuring, no long-term studies have been published to date.¹⁴

Complications

The safety of OS with regard to perioperative complications has also been investigated extensively. In the Society of Gynecologic Oncology of Canada (GOC) Clinical Practice Guideline, it has been stated that performing opportunistic salpingectomy at the time of hysterectomy for benign gynaecologic disorders does not increase complication rates, length of hospital stay, or overall recovery time but does lead to a minor increase in surgical time.¹⁹ Hanley et al. suggested that hysterectomy with bilateral salpingectomy is significantly increasing in the United States and is not associated with increased risks of postoperative complications.²⁴

A population-based retrospective cohort study of 43,931 women in British Columbia, Canada, during 2008-2011, investigated the outcomes of OS at the time of hysterectomy or for sterilization.¹⁰⁶ Minimal additional surgical time was required for hysterectomy with salpingectomy (+16 minutes) and bilateral

salpingectomy for sterilization (+10 minutes) compared with hysterectomy alone or tubal ligation, respectively. There were no significant differences with regard to risks of hospital readmission or blood transfusions in the OS group. Overall, the data strongly support the incorporation of OS into gynaecologic surgery for benign indications as a safe strategy to reduce the risk of EOC. Another author of the same group reported no differences in minor complications between women who undergo opportunistic salpingectomy and women who undergo hysterectomy alone or tubal ligation, except for a slightly increased need for analgesic medication in the immediate 2 weeks after discharge.¹²⁰

Retaining the fallopian tubes at the time of hysterectomy increases the risk of subsequent reoperation for tubal pathology.¹⁹ Opportunistic salpingectomy eliminates the risk of subsequent tubal pathology like hydrosalpinx and, in the case of tubal sterilization, ectopic pregnancy - an advantage over conventional tubal sterilization methods such as partial salpingectomy, banding or coagulation. Hydrosalpinx is the most frequent complication following hysterectomy without OS, and occurs in 35.5 % of patients requiring repeat surgery in 7.8% of patients.^{121,122} Other complications include pelvic inflammatory disease, salpingitis, benign fallopian tube tumours, and tube prolapse.¹²³⁻¹²⁸ Many of these conditions require treatment with salpingectomy and could be avoided by performing OS at the time of hysterectomy and instead of tubal ligation.¹⁴

Surgical technique and timing of opportunistic salpingectomy

According to standard clinical guidelines, the fallopian tube should be completely removed from its fimbriated end and up to the uterotubal junction during salpingectomy. There is no need to remove the interstitial portions of the tubes. Any fimbrial attachments on the ovary should be cauterized or removed. Complete salpingectomy is preferred over removal of fimbrial part only because precursors to fallopian tube cancer or

ovarian cancer can be found throughout the fallopian tube.¹²⁹ However, if complete salpingectomy is not feasible, then removing as much of the fallopian tubes as possible, excluding the interstitial portion, still may have value.¹³⁰

An online portal for obstetrics and gynaecology has described in detail the techniques for opportunistic salpingectomy which is summarized below.¹³¹

Laparotomy

Salpingectomy at the time of abdominal hysterectomy should be performed prior to hysterectomy because it allows for complete removal of the entire fallopian tube without the need to re-isolate any surgical pedicle. The small vessels inside the mesosalpinx that lie between the ovary and fallopian tube should be isolated. These vessels are branches of the ovarian and uterine arteries and may provide additional blood supply to the ovaries. Alternatively, a monopolar electro surgery device with coagulation current or an electrosurgical vessel sealing device can be used. These devices should be placed immediately adjacent to the tube in order to cauterize and transect the mesosalpinx. Once detached from the mesosalpinx, the fallopian tubes can be left attached to the uterus as the hysterectomy is then performed and can be removed en bloc with the uterus.

Laparoscopy

Both traditional and robotic approaches to laparoscopy allow for bilateral salpingectomy at the time of hysterectomy. Any laparoscopic instrument that allows for electrosurgical vessel sealing and transection of tissue, can be used to dissect across the mesosalpinx. Alternatively, a monopolar electrosurgery device can be used to cauterize the mesosalpinx before transection with endoscopic scissors. As in the open approach, the fallopian tubes can be left attached to the uterus while the hysterectomy is performed and removed as a single unit once the hysterectomy is complete.

Salpingectomy at the time of vaginal hysterectomy is often the most challenging of these procedures. In this situation, the hysterectomy is performed as usual up to the level of the “triple pedicles.” At that point, the first triple pedicle - incorporating the utero-ovarian ligaments, the fallopian tubes, and the round ligaments - is clamped and transected from the uterus. Next the feasibility of transvaginal salpingectomy is evaluated by gently turning the clamp on the triple pedicle in order to make an anatomic assessment. In a technique described by Kho and colleagues, the round ligament can first be divided to allow better mobilization of the adnexa and access to the proximal fallopian tube.¹³² Leaving the triple pedicle clamped rather than suture-ligating it allows for the clamp to become a handle with which gentle traction and manipulation of the tube can be done. Once identified, the fimbriated end of the fallopian tube should be brought into the operative field with a Babcock clamp. Fimbriated end should be freed from the ovary by clamping, transecting, and ligating isolated vascular pedicles of the mesosalpinx, or with monopolar cautery or an electrosurgical vessel sealing device. Once the isthmic portion of the tube is reached, a second large clamp is placed just cephalad to the large clamp that contains the triple pedicle to incorporate only the utero-ovarian ligament and the round ligament, leaving the fallopian tube free. The first large clamp can then be removed, allowing for completion of the salpingectomy while the utero-ovarian ligament and the round ligament remain clamped at all times. Then the fallopian tube is removed in its entirety. The contralateral triple pedicle is then clamped and transected, and the uterus is removed before performing contralateral salpingectomy. Then the contralateral salpingectomy is completed in a similar fashion after removing the uterus.

Postpartum salpingectomy and salpingectomy at time of Cesarean delivery appear feasible and safe. Although there effectiveness of complete salpingectomy as a method of sterilization is not validated till date, in previous studies postpartum

partial salpingectomy and interval partial salpingectomy were found to have a 7.5 and 20.1 cumulative probability of pregnancy per 1,000 procedures, respectively, in the United States.¹³³ Two studies found an increased surgical time of 9-13 minutes for bilateral salpingectomy at time of Cesarean delivery compared to tubal ligation either with suture ligation or cauterization; otherwise, there were no differences in blood loss or complications.^{134,135} Another retrospective study of 149 women who underwent sterilization at the time of Cesarean delivery showed no difference in surgical time for either group, as well as no difference in blood loss or complications like infection, reoperation, and readmission. An electrothermal bipolar vessel sealing system was used for the 50 patients who underwent salpingectomy and modified Pomeroy technique was used for the 99 patients who had a tubal ligation.¹³⁶ In 2018, one randomized controlled trial also reported an increase in operative time of 15 minutes in the salpingectomy group and there were no adverse events related to the sterilization procedure reported in either group.¹³⁷ Current data on salpingectomy during post partum sterilization procedures are limited to a few small studies which reported longer durations of surgery (12-17 minutes) and a small increase in blood loss (50 mL) for postpartum salpingectomy when compared with postpartum bilateral tubal ligation or postpartum tubal occlusion.^{135,138} In another study involving 194 patients with salpingectomies at time of Cesarean delivery, 97 had salpingectomies by bipolar electrocautery and 97 by suture ligation. In bivariate analysis, salpingectomy by bipolar electrocautery was associated with less estimated blood loss and shorter operating time. There were no statistical differences in length of stay, readmission, emergency room visits after discharge, or number of surgeons involved.¹³⁹

Current trend

American Society of Clinical Oncology (ASCO) commented in their Annual Meeting 2020 that OS for ovarian cancer prevention has rapidly diffused

into clinical practice with the speed of adoption bolstered by recommendations from national societies.¹⁴⁰ The uptake of OS has been studied in depth in the Canadian state of British Columbia where the campaign was first initiated and was then adopted across Canada more widely.¹⁴ McAlpine et al.¹⁰⁶ reported that the proportion of OS increased from 8% in 2008 to 63% in 2011, and the proportion of sterilizations by salpingectomy increased from 0.5% in 2008 to 33% in 2011. Their team has recently extended this analysis to 2013 and found that 75% of all hysterectomies without oophorectomy included opportunistic salpingectomy and 48% of all sterilizations were done by salpingectomy in 2013.¹⁴

Chen et al.⁶⁵ reported that the overall rate of bilateral salpingectomy in women with benign gynecological disease gradually increased in Tianjin Medical University Cancer Institute and Hospital in China from 2007 to 2017 (from 22.02% to 60.22%), which showed approximately threefold increase in a decade. A similar trend of increase in removal of adnexal structures was noted in a National Population-Based Study conducted in Australia including data from 2001-2015.¹⁴¹ In the United States, the rate of bilateral salpingectomy at the time of Cesarean section has also increased rapidly between 2015 and 2018, replacing tubal ligation as the most common type of sterilization performed with Cesarean delivery. However, the higher surgical morbidity in the bilateral salpingectomy group than the bilateral tubal ligation group observed in their study warrants further investigation.¹⁴²

However, salpingectomy can be more challenging at VH and this has a potential to influence the choice of approach for hysterectomy. De Cure and Robson showed low rates of adnexal removal associated with VH in their study. They also commented that the technical challenges in performing adnexal surgery at the time of VH are well-recognized and less appealing.¹⁴¹ In a multicenter, prospective study on patients undergoing planned vaginal hysterectomy with

bilateral salpingectomy rates of salpingectomy were highest for laparoscopic and lowest for vaginal hysterectomy.¹⁴³ They concluded that vaginal salpingectomy is feasible in the majority of women undergoing vaginal hysterectomy and it increased operating time by 11 minutes and blood loss by 6 mL. They also commented that women with prior adnexal surgery or uterine fibroids should be counseled about the possibility that removal may not be feasible. However, over the past few years salpingectomy during vaginal hysterectomy has been increasingly utilized by gynaecology surgeons in the USA and the rate increased from 34.4% in 2014 to 46.8% in 2016.¹⁴⁴ Giraudet et al. demonstrated a simple technique to safely perform opportunistic salpingectomy during vaginal hysterectomy and reported success in all attempts (more than 60 cases).¹⁴⁵

Physician attitudes towards opportunistic salpingectomy

There have also been several surveys assessing physician attitudes towards OS. A Canadian survey of obstetricians and gynaecologists as early as 2013 revealed that 90% had heard of OS, but 37% were unaware of the evidence supporting the hypothesis that HGSC originates in the fallopian tube and 38% were unsure whether there would be any population benefit to performing OS.¹⁴⁶ Whereas a survey of physicians in American institutions with Obstetrics & Gynecology Residency Programs in 2013 reported that 54% of physicians perform OS with hysterectomy. The 46% of physicians who did not commonly perform OS reported that they did not believe there was any benefit. While 58% of practitioners believed it was the most effective method of sterilization after age 35 and they only chose this method in patients in whom a previous tubal sterilization has failed or because of tubal disease.¹⁴⁷ A similar survey of Irish Obstetricians and Gynecologists around same time reported that 90% would consider OS at the time of abdominal hysterectomy and 73% would consider OS for female sterilization.¹⁴⁸ An anonymous online survey was sent to all active Royal Australian and New Zealand College of Obstetrics and

Gynaecology (RANZCOG) fellows in Australia in 2015 which revealed that 70% of respondents had been offering or discussing OS to women undergoing gynaecological surgery for benign indications, usually at the time of abdominal (96%) or laparoscopic (76%) hysterectomy. Main reasons for not offering OS were insufficient evidence to benefit the woman (36%) or being unaware of recent evidence (33%).¹⁴⁹ In 2016 a survey was emailed to 300 members of the American College of Obstetricians and Gynecologists. It revealed that only 23% respondents understood the risk-reducing benefit of bilateral salpingo-oophorectomy. About 75% performed salpingectomy during hysterectomy and 26-53% used for sterilization. Main concerns were increased operative time and complications though minor.¹⁵⁰ In 2017 current practice in Japan with respect to performing opportunistic bilateral salpingectomy during gynaecological surgery for benign disease for ovarian cancer prevention was investigated. Only 54.0% of responding institutions performed opportunistic bilateral salpingectomy and just 6.8% of the institutions were willing to participate in randomized controlled trials to validate this method for reducing the incidence of ovarian cancer. The study commented that The Japan Society of Obstetrics and Gynecology (JSOG) - Gynecologic Tumour Committee would announce its opinion on salpingectomy for ovarian cancer prevention to all JSOG members and would develop a system for monitoring the number of OS procedures in Japan.¹⁵¹ An anonymous online survey in 2019 among the consultant obstetrician/gynaecologists in Northern Ireland concluded that there are still significant gaps in knowledge regarding STIC among consultants in Northern Ireland, which affects their willingness to consider opportunistic salpingectomy at the time of other operations. If these gaps and their concerns are addressed, there may be an impact on the potential benefit of performing this procedure in reducing the incidence of HGSC.¹⁵² A nationwide cross-sectional study through anonymous online survey was conducted in all hospitals in the Netherlands in 2019. Current practice of

discussing and performing the OS varied widely. The study revealed that on individual patient level, a vaginal approach of hysterectomy, negative family history for ovarian cancer and the presence of firm adhesions were suppressive factors for the OS.

Counselling and patients' perspective

Given the opportunistic nature of OS, several international societies have issued guidelines which recommend to discuss OS with all women undergoing abdominal surgery after completion of childbearing.^{153,154} Counselling is of fundamental importance before opportunistic salpingectomy as in any other surgery. Women should be clearly explained the role of this preventive approach. The surgeon and patient should discuss the potential benefits of the removal of the fallopian tubes during a hysterectomy in women at population risk of ovarian cancer who are not having an oophorectomy. It is recommended that counselling women who are undergoing routine pelvic surgery about the risks and benefits of salpingectomy should include an informed consent discussion about the role of oophorectomy and bilateral salpingo-oophorectomy. When counselling women about laparoscopic sterilization methods, obstetricians can communicate that bilateral salpingectomy can be considered a method that provides effective contraception. The risks and benefits of salpingectomy should also be discussed with patients who desire permanent sterilization.²⁵ Patients should be counselled that salpingectomy eliminates tubal reversal as an option for those women who seek fertility options later and their only option would be then to go for IVF.¹⁵⁵

Adequate information on all aspects of any surgery is essential to enable patient participation in decision making. A mixed-method study between 2019 and 2020 throughout the Netherlands involving both patients and professionals to evaluate their individual perspectives and awareness regarding this issue revealed that from a patients' perspective, the most

important barrier in deciding whether or not to undergo OS is that they are simply unaware of its existence. Patients also lack knowledge on the advantages, disadvantages and the magnitude of the intervention, which prevents a well-informed decision. They recommended that informed consent and counselling content should be based on the patients' knowledge needs and fully explain all aspects that could potentially influence the decision for patients.¹⁵⁴

They should be informed that bilateral salpingo-oophorectomy that causes surgical menopause reduces the risk of ovarian cancer but may increase the risk of cardiovascular disease, cancer other than ovarian cancer, osteoporosis, cognitive impairment, and all-cause mortality.³⁰ The risk of ovarian cancer after hysterectomy with ovarian conservation is 0.1-0.75%.¹⁵⁶ In the Nurses' Health Study, death from ovarian cancer after conservation of the fallopian tubes and ovaries was 0.03%.²⁶ Again the benefits of ovarian conservation decrease with age, and there is little benefit after age 65 years.¹⁵⁷

Although many types of epithelial ovarian cancers may originate from the fallopian tube, some types of epithelial ovarian cancer and nonepithelial ovarian cancer, such as germ cell tumours and sex-cord stromal tumours, primarily arise from the ovary rather than the fallopian tube. Thus, although opportunistic salpingectomy offers the opportunity to significantly decrease the risk of epithelial ovarian cancer, it does not eliminate the risk of ovarian cancer entirely. Obstetrician-gynaecologists should counsel women who have undergone salpingectomy of potentially relevant signs and symptoms of ovarian cancer.²⁵

Conclusion

The fallopian tube undoubtedly plays a primary role in the pathogenesis of EOC and its removal should be effective to some extent in the prevention of this disease. For women at population risk of ovarian cancer, opportunistic salpingectomy presents a promising approach to

reducing incidence and mortality from ovarian cancer, and recommendations to integrate it into routine gynaecologic practice are increasingly common. Yet more population-based studies are required to evaluate whether opportunistic salpingectomy can reduce the incidence of high-grade serous cancers.¹⁹ While preliminary safety and efficacy data are very reassuring, there remain some unanswered questions. Specifically, we need more data on the impact of OS on ovarian function, which is being examined both through several randomized controlled trials and cohort studies in order to determine if OS accelerates menopause. Hanley et al. stated that not surgical intervention is not advocated solely for the purposes of salpingectomy nor change in surgical approach if the planned route for the required gynaecologic surgery cannot achieve salpingectomy.¹⁴

In summary, opportunistic salpingectomy is a safe intervention in the short term, when done concurrently with hysterectomy or instead of tubal ligation. Additional research is needed to establish the optimal lower age limit to undergo opportunistic salpingectomy and to evaluate effectiveness and safety in the postmenopausal population, especially to determine the optimal age to opt for salpingo-oophorectomy instead of salpingectomy.

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