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REVIEW

Current Updates on Salpingectomy for the Prevention of Ovarian Cancer and Its Practice Patterns Worldwide

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Abstract A paradigm shift of the origin of ovarian cancer to fallopian tube has brought more focus on bilateral salpingectomy as a preventive method for ovarian cancer. Bilateral salpingectomy has shown a dramatic reduction in the risk of ovarian cancer. Bilateral salpingo-oophorectomy has been a long-used practice to prevent ovarian cancer, but it brings surgical menopause and an increased mortality rate to women undergoing such a surgery at the age of <47.5. With the prophylactic bilateral salpingectomy, however, the ovarian function remains unaltered. Recent studies have shown that prophylactic salpingectomy was helpful not only in preventing high-grade serous type ovarian cancer, but also in decreasing adnexal pathologies. With the publication of committee opinion, more practitioners have accepted this proposal, but some are more concerned about its disadvantages. This review illustrates the latest updates on salpingectomy as a preventive method for ovarian cancer, including its advantages and disadvantages, clinicians' opinions, public opinions, so as to find out Obstetricians' and Gynecologists' practice pattern related to opportunistic salpingectomy worldwide.

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OVARIAN cancer is the fifth leading cancer in women and of all gynecological neoplasms, and it has the highest mortality rate.¹ In the USA, it is estimated that 22 280 new cases will be diagnosed with ovarian cancer in 2016 and 14 240 deaths are expected.²

In an annual screening with CA125 and trans-vaginal ultrasound in 35 000 women among which, 70% of screen-detected ovarian cancer women were reported with an advanced stage of disease.³ The aggressiveness of this disease is a matter of concern for its early detection, treatment and prevention. The risk of ovarian cancer increases in women who have ovulated more over their lifetime, like those who never have children, whose ovulation started at a younger age, who reached menopause late, and those with a family history of ovarian cancer and being breast cancer mutation (BRCA) carriers. It was found that the use of oral contraceptive pills lowered the risk of ovarian cancer with $OR=0.70$ (95%CI 0.52-0.94) in hospital studies and $OR=0.66$ (95%CI 0.55-0.78) in population studies.⁴ The presence of serous intraepithelial neoplasm in the fallopian tube in women with BRCA1 and BRCA2 mutations who had undergone bilateral salpingo-oophorectomy (BSO) has brought more curiosity to researchers. Due to the site of tumor being the ovary, fallopian tubes were always neglected. After the lesion was discovered in women with heredity predisposition, various studies started emerging stating about the cells origin of ovarian cancer shifting from the ovary to the fallopian tube.⁵⁻⁶ Since the focus was taken on the fallopian tube, a few clinicians started conducting bilateral salpingectomy in women undergoing hysterectomy for benign causes, and even in women with genetic mutation who deny for BSO, and this resulted in significant decrease in ovarian cancer. Bilateral salpingectomy, unlike BSO, does not hamper the quality of life. Ovarian blood supply and ovarian function remain unaltered if the surgery is performed cautiously. Clinicians still hesitate to discuss with patients about the benefit of bilateral salpingectomy. And many clinicians are still unaware about the new cancer pathogenesis and the risk reducing strategy.

Our objective of this study is to review the latest studies done on salpingectomy as a preventive method for ovarian cancer, including the advantages and disadvantages, latest clinician opinions, public opinions on this matter, and to find out Obstetricians' and Gynecologists' practice patterns related to opportunistic salpingectomy worldwide.

THE ORIGIN OF OVARIAN CANCER, IS IT THE FALLOPIAN TUBE?

The origin and pathogenesis of ovarian cancer are poorly understood. Evidence from different research hints that the origin of ovarian cancer is from the fallopian tube rather than the ovary. According to the dualistic model of carcinogenesis, epithelial ovarian cancer has been divided into two categories: type I and type II. Type I tumors include low-grade serous, low-grade endometrioid, clear cell, and mucinous carcinomas; whereas type II tumors consist of high-grade serous carcinomas, high-grade endometrioid carcinomas, malignant mixed mesodermal tumors, and undifferentiated carcinomas. Type I tumors are genetically stable and undergo KRAS, BRAF, PTEN, PIK3CA, CTNNB1, ARID1A and PPP2RIA mutations, but rarely TP53 mutation; Type II tumors are mainly high grade serous carcinoma (HGSC), highly unstable, and undergo TP53 mutation. BRCA inactivation occurs in up to 40%-50% of HGCS, but it has not been reported in type I tumors.⁷ It has been proposed that low-grade and high-grade serous tumors arise from the implantation of the epithelium from the fallopian tube but not the ovary. During ovulation, fimbria comes close in contact with ovary, and tubal epithelial cells are implanted on the disrupted ovarian surface and thus to form cortical inclusion cysts.⁶ Endometrioid and clear cell tumors are associated with endometrial tissue implanted in the ovary *via* retrograde menstruation.⁸ Mucinous and transitional tumors are said to arise from the transitional-type epithelium nests at tubal-epithelial junction.⁵⁻⁶

HGSC is the most common subtype of ovarian cancer, and we will be discussing in detail about its fallopian origin. Firstly, the gene expression of HGSC is closely related to fallopian tube rather than ovarian epithelial surface. Immunohistochemical study showed that HGSC expressed PAX8, a müllerian marker, but not calretinin, a mesothelium marker,⁶ whereas ovarian surface epithelium is mesothelium in origin. HGSC shows TP53 mutation, and normal fallopian tubes also show TP53 signatures with TP53 mutation occasionally occurring.⁶ Secondly, serous tubal intraepithelial carcinoma (STIC) was identified in a specimen of women with hereditary predisposition to ovarian cancer.⁹ Previously fallopian tube was not carefully examined in ovarian cancer patients, so lesions in the fallopian tube were missed. After careful examination, it was found that STICs were even seen in 50%-60% of women without known BRCA mutation.¹⁰⁻¹¹ Concomitant presence of TP53 mutation in women with STIC and HGSC made it clear that HGSC might have arisen from the fallopian tube but not

from the ovary. STIC and HGSC also co-expressed p16, FAS, Rsf-1 and cyclin E1.¹² Like other precancerous lesions, STIC also showed short telomere.¹³ Dysplastic lesion in the fallopian tube was commonly found in the fimbriated end of the fallopian tube rather than in other segments.¹⁴ Furthermore, Kim *et al*¹⁵ have provided further evidence of the fallopian tube as the source of HGSC in their mouse model. They found that, HGSC developed in mice that underwent bilateral oophorectomy and had fallopian tubes intact, but did not develop in mice that underwent bilateral salpingectomy and had ovaries intact. Not only HGSC but also other epithelial ovarian cancers are thought to be derived from the fallopian tube and endometrium, but not directly from the ovary. With all this evidence, it is possible to relate fallopian tube to be the origin of ovarian cancer, mainly for the high-grade serous type.

EVIDENCE SHOWING THE BENEFITS OF PROPHYLACTIC BILATERAL SALPINGECTOMY

In consideration of this paradigm shift of the origin of ovarian cancer to fallopian tube, clinicians started to try prophylactic bilateral salpingectomy to prevent ovarian cancer. Initially in 2014, Lessard-Anderson *et al*¹⁶ studied the effect of excisional tubal sterilization technique on the risk of serous epithelial ovarian cancer (EOC) and primary peritoneal cancer (PPC), in which, from 1966 to 2009, 194 cases of EOC and PPC and 388 cases of the control group were included. The rates of tubal sterilization were 72% (14/194) in the study group and 11.9% (46/388) in the control group. Among those who had tubal sterilization, excisional tubal sterilization was received by 36% (5/14) of the study group and 55% (25/46) of the control group, and complete salpingectomy was received by 13% (6/46) of the control group and 0 case in the study group. Excisional tubal sterilization alone showed 63% decrease in the risk of EOC and PPC. Then in 2015, Madsen *et al*¹⁷ further studied the effect of bilateral salpingectomy on reducing the risk of epithelial ovarian cancer, comprising 13 241 cases with epithelial ovarian cancer and 194 689 cases of the control group. In the disease group, 89 underwent unilateral salpingectomy and 17 underwent bilateral salpingectomy. In the control group, 1382 underwent unilateral salpingectomy and 411 underwent bilateral salpingectomy. Bilateral salpingectomy was associated with 42% decrease in the risk of epithelial ovarian cancer; but in the unilateral salpingectomy group, the risk reduction was smaller and not significant. Even though there was limited number of

bilateral salpingectomy cases, it was associated with a decreased risk of epithelial ovarian cancer. Further Falconer *et al*¹⁸ studied a cohort of women in Sweden from 1973 to 1996 and followed through 2009, with the mean age of 35.9 years and mean follow-up of 23.1 years, including 98 026 females who had hysterectomy. Among them, 37 348 had hysterectomy with BSO, 34 433 had salpingectomy, and 81 658 had sterilization. Women with hysterectomy and concomitant salpingectomy constituted a small group ($n=2646$) and were excluded from analysis. A significant reduction in the risk of ovarian cancer was seen in women undergoing salpingectomy. Those who underwent unilateral salpingectomy showed a reduction with $HR=0.71$ (95% $CI=0.56$ to 0.91), and those who had bilateral salpingectomy showed 50% of reduction in the risk of ovarian cancer with $HR=0.35$ (95% $CI=0.17$ to 0.73). Kwon *et al*¹⁹ further focused on the risk of ovarian cancer in patients who underwent hysterectomy alone, who had hysterectomy with salpingectomy and who had hysterectomy with BSO for benign gynecologic conditions or surgical sterilization. In total, 28 000 cases underwent hysterectomy; 270 cases were diagnosed with ovarian cancer after hysterectomy alone; 167 cases were diagnosed with ovarian cancer after hysterectomy with salpingectomy, which showed a 38.1% reduction in the risk of ovarian cancer in women who underwent hysterectomy with salpingectomy compared to those with hysterectomy alone. Hysterectomy with BSO showed a dramatic decrease in ovarian cancer with the reduction of 88.1%. But when death due to premenopausal BSO was compared, 934 cases died after BSO and 8 cases died after salpingectomy. Kwon even compared the risk of ovarian cancer between the two sterilization groups: there was a 29.2% reduction in ovarian cancer posterior to salpingectomy, compared to tubal ligation. Vorwerk *et al*²⁰ researched in 540 premenopausal women undergoing hysterectomy for benign causes. Among them, 127 patients underwent prophylactic bilateral salpingectomy. Postoperatively, in 60 women who did not undergo prophylactic bilateral salpingectomy, the occurrence of adnexal pathologies was noted, in which 33 cases had ovarian cyst, 18 adnexitis, 8 hydrosalpinx and 1 pyosalpinx. Hysterectomy related surgical interventions were higher in the group who did not undergo prophylactic bilateral salpingectomy. Study showed that, preservation of fallopian tube in premenopausal women increased the risk of adnexal pathologies and even increased the risk of re-surgery. Bilateral salpingectomy not only can reduce ovarian cancer but also can reduce some benign ovarian and fallopian tube diseases.

Tubal ligation has widely been performed for permanent contraception. Previously, tubal ligation has also shown some reduction in the risk of ovarian cancer, especially the ovarian endometrioid subtype.²¹ Cibula *et al*²² conducted research on tubal ligation and the risk of ovarian cancer, which reported an overall $HR=0.69$ ($95\%CI=0.64$ to 0.75). Rice *et al*²³ studied the risk of ovarian cancer with tubal ligation, which showed $HR=0.67$ ($95\%CI=0.49-0.90$) when tubal ligation was done at the age of <35 . Though these two studies showed reductions in the risk of ovarian cancer, emerging theories on initial fimbrial involvement in ovarian cancer make us suspicious about its prevention of high-grade serous type ovarian cancer. Danis *et al*²⁴ compared salpingectomy and tubal ligation in respect to estimated blood loss, duration of surgery and complications. He involved 64 patients who had undergone tubal ligation and 16 patients with salpingectomy; no difference was found between these two groups.

Even though BSO has shown to reduce the risk of ovarian cancer, it also affect the quality of life. Women were more osteoporotic, more prone to coronary artery diseases, and hypoactive sexual desire was noticed. In a Nurse Health Study, it suggested that oophorectomy before age 47.5 may be associated with increased risk of death from cardiovascular disease and even increased risk of dementia and cognitive impairment.²⁵⁻²⁸

Kwon *et al*²⁹ concluded that in BRCA carriers, bilateral salpingectomy with delayed oophorectomy was effective in terms of quality-adjusted life expectancy.

EVIDENCE SHOWING THE RISKS WITH PROPHYLACTIC BILATERAL SALPINGECTOMY

Even at knowing the reduction in the risk of ovarian cancer by bilateral salpingectomy, whether or not to carry it out as a preventive method is a big question. What about its side effect? Actually this question was first addressed in animal models. Zhao *et al*³⁰ experimented on monkeys to see their ovarian function after bilateral (B/L) salpingectomy. The result showed all salpingectomized monkeys had at least one corpus luteum with a distinct stigma on one ovary, same as the result of sham-operated monkeys, and no demonstrable endocrine changes were seen. Halme *et al*³¹ experimented on nine rabbits undergoing B/L salpingectomy and other nine undergoing sham operation. They found there were no significant difference in progesterone level, the means of the number and the weight of corpus luteum.

Further research was done to show the effect of salpingectomy on ovarian function, Morelli *et al*³² enrolled 79 patients who underwent only total abdominal hysterectomy (TAH) and other 79 patients who underwent TAH with salpingectomy. Their study revealed no statistical difference between the two groups in terms of anti-mullerian hormone (AMH), follicle stimulating hormone (FSH), antral follicle counts (AFC) and mean ovarian diameters. Then Findlay *et al*³³ further focused on hormonal changes and blood loss by salpingectomy. In this research, 15 patients underwent laparoscopic hysterectomy, and another 15 patients received laparoscopic hysterectomy plus salpingectomy; no difference in AMH, mean operation time and mean blood loss was found between the two groups. Recently, Atalay *et al*³⁴ compared the ovarian function between the group receiving TAH plus bilateral salpingectomy (TAH-BS) and the group receiving total laparoscopic hysterectomy plus bilateral salpingectomy (TLH-BS). The ovarian function was evaluated before and 6 months after the surgery. Postoperatively luteinizing hormone (LH), FSH and inhibin B decreased in both groups. A significant decrease was seen in AMH and ovarian function in the TAH-BS group compared to the TLH-BS group. Since this research was based on two different surgical procedures, we cannot conclude if hysterectomy or salpingectomy alone decreases the ovarian function. To show the effect of salpingectomy on artificial reproductive technology, Dar *et al*³⁵ evaluated ovarian function before and after salpingectomy. It showed no significant changes in human menopausal gonadotropin (HMG) used in the cycles, pre-ovulatory concentration of estrogen, the number of oocytes retrieved and the quality of the embryo. After salpingectomy, implantation rate was 23.07% and clinical pregnancy rate was 19.23% in patients who underwent *in vitro* fertilization (IVF). Qin *et al*³⁶ also analyzed 13 studies and concluded that salpingectomy did not affect ovarian function, ovarian response to gonadotropin stimulation, or the outcome of IVF embryo transfer (IVF-ET) in the short run. It may, however, impair ovarian reserve in the long run. As mentioned above, animal models and all other research showed no significant change in hormone level and ovarian function when salpingectomy was performed carefully. Although bilateral salpingectomy is much more reliable to prevent various ovarian diseases, we have to be cautious about the risk that is brought up by the surgery, such as bleeding, leaking, infection, more cost, more hospital days and post-surgery morbidity. Since no definitive long term effect has been researched, more studies are needed to

find the long term effect of bilateral salpingectomy.

RECENT PERCEPTION ON THE PRACTICE OF BILATERAL SALPINGECTOMY

Even though it is almost clear that bilateral salpingectomy might prevent the development of ovarian cancer, it has always been a controversial matter. Do patients want bilateral salpingectomy as preventive method or permanent contraception? Do Obstetricians and Gynecologists want to recommend bilateral salpingectomy as a preventive method or permanent contraception?

As patients' compliance, in a study on the public perception of 100 women done by Kang *et al*,³⁷ regarding knowledge about ovarian cancer and bilateral salpingectomy, 71% of the females did not have any knowledge about the risk of ovarian cancer; 87% did not have any information about bilateral salpingectomy; 98% wanted to get informed about the benefit of bilateral salpingectomy while going through any gynecological surgery. The limitation of this study was the small number of participants and the location of urban areas where it was conducted. Thus, clinicians should discuss with patients about the benefits of bilateral salpingectomy before undergoing any gynecological surgeries for benign causes, and raise awareness of patients about the risk of ovarian cancer.

A statement released in 2011 by the Society of Gynecologic Oncology of Canada encouraged physicians to discuss with patients about the pros and cons of prophylactic bilateral salpingectomy at the time of hysterectomy or tubal ligation.³⁸ American College of Obstetrics and Gynecology Committee published their opinion in 2015,³⁹ and suggested that surgeons should inform patients about the advantages of bilateral salpingectomy before performing hysterectomy in high-risk patients who deny oophorectomy and permanent sterilization. In addition, they considered bilateral salpingectomy to be an effective method for contraception. They even mentioned that minimal invasive technique should be confined just to salpingectomy, and vaginal hysterectomy should not be replaced by laparoscopic hysterectomy.

With regard to society opinion, committee opinion and the benefits of bilateral salpingectomy, a lot of clinicians started performing this procedure. Regarding clinicians' opinions, lot of survey started blooming out. In 2013, Gill *et al*⁴⁰ reported that 54.3% of clinicians performed bilateral salpingectomy during hysterectomy for benign causes, among which, 75% intended to reduce the risk of ovarian cancer, 49.1% to avoid repeated surgery, 48.3% to avoid the risk of developing hydro-salpinx, and 30.2% to decrease

the risk of pelvic pain. Among the remaining patients who did not perform salpingectomy, 69.4% mentioned that there was no benefit for decreasing the risk of ovarian cancer, 40% believed it increased operative time, 34.1% thought there would be increased intraoperative complications, and 23.5% did not believe it would decrease the risk of ovarian cancer. This survey also questioned clinicians about their perception on the use of salpingectomy as a permanent sterilization procedure. The result revealed 58.3% of clinicians believed that salpingectomy was the most effective permanent form of sterilization for women older than 35. Another survey done in Canada by Reade *et al*,⁴¹ involved 757 physicians, and only 192 physicians responded the survey. The result showed 55% of the clinicians did not perform salpingectomy, and among them, 51% believed that there was no benefit, 36% thought it increasing surgical morbidity, 19% believed it increasing operative time, and 8% regarded it increasing surgical complexity. Earlier, most clinicians were unaware of the benefit of bilateral salpingectomy; but in recent years, clinicians started performing it worldwide. In 2015, a similar survey was done in Australia. Totally, 1490 clinicians were questioned about the opportunistic bilateral salpingectomy (OBS) during gynecological surgeries for benign causes, and only 382 clinicians responded. Finally, 269 clinicians would discuss or perform OBS in the women with a low risk of ovarian cancer before undergoing any gynecological surgery for benign causes. In addition, 96% of clinicians during counseling for abdominal hysterectomy and 76% before laparoscopic hysterectomy, would offer or discuss OBS.⁴² In a survey done in Italy by Venturella *et al*,⁴³ most of the clinicians performed bilateral salpingectomy. There were 391 out of 477 clinicians who performed prophylactic bilateral salpingectomy, and among them, 371 performed to reduce the risk of ovarian and peritoneal cancers; 86 out of 477 clinicians did not perform salpingectomy, and among them, 47 thought that there was no benefit, 24 thought there was a risk of repetitive surgery, 19 believed it increasing the risk of intraoperative complications, 14 considered it increasing operative time, and 9 disbelieved the fact of reducing the risk of peritoneal and ovarian cancers. The clinicians were asked if they had information on the paradigm shift of the pathogenesis of ovarian cancer and the possibility of salpingectomy as a risk reducing strategy. The result displayed that, 65.44% of the clinicians were aware of the literature and safety data published, 20.95% knew about the literature but were unaware of the safety data published, 7.55% had heard it in the conference, 4.53% had never heard about prophylactic bilateral salpingectomy and 1.51% were asked about it by

patients. Lately, on this topic, Garcia *et al*⁴⁴ showed the increasing rate in the practice of salpingectomy recent years in the United States. Patients aged over 18 years old were involved. From June 2011 to May 2014, among 12 143 patients receiving hysterectomy, 7498 underwent hysterectomy with salpingectomy, and the rate of salpingectomy was increased from 14.7% to 72.7%. According to the clinicians' view, 54.0% did not have any barriers performing, 36.0% reported difficulty in accessing fallopian tube, 3.0% believed it increased complications, 2.1% did not mention, 2.1% had no evidence found, 0.7% believed it potentially decreased ovarian reserve, 0.7% complained of increased operating room time, 0.7% thought it increased counseling time, and 0.7% lack of equipment to perform salpingectomy. The change in the trend towards the use of salpingectomy is seen, and clinicians are more aware of the fact about the benefit of salpingectomy in current days. Garcia *et al*⁴⁴ even reported that, the median estimated blood loss was lower, and even the operating time was shorter, in the salpingectomy group when compared with the group of hysterectomy alone. The only limitation of this study was the selection bias due to the low response rate of the clinicians. Clinicians' opinions have been compared below (Table 1). Due to a decrease in the trend of total vaginal hysterectomy and an increase in trend of laparoscopic assisted vaginal hysterectomy, more bilateral salpingectomy is being performed worldwide. A large population based study conducted by Mikhail *et al*⁴⁵ compared the current practice of concurrent bilateral salpingectomy during total vaginal hysterectomy (TVH) with laparoscopic-assisted vaginal hysterectomy (LAVH) in the United States. It was found that, from 1998 to 2004,

bilateral salpingectomy during TVH increased from 2% to 14%, with 42.8% annual increase, and it remained stable from 2004. Moreover, the rate of bilateral salpingectomy with LAVH increased nearly 15% each year during the entire study period.

In conclusion, in premenopausal women who undergo hysterectomy for benign uterine pathologies, bilateral salpingectomy could reduce the lifetime risk of developing HGSC. It not only helped in reducing ovarian cancer, but also helped in reducing adnexal pathologies. There was no difference in the values of AMH, FSH, LH, AFC, and mean ovarian diameter between the patients undergoing hysterectomy and the patients undergoing hysterectomy with bilateral salpingectomy, which indicates that ovarian function remained unaltered when bilateral salpingectomy was performed carefully. Bilateral salpingectomy might give a better quality of life, as it avoids the risk of premature menopause. The proportion of clinicians who incorporated bilateral salpingectomy varies from 45% to 86% in various countries. And 90% of clinicians performed the procedure to reduce the risk of ovarian cancer. There is still a small percentage of clinicians that are unaware about the new pathogenesis of ovarian cancer and about the role of bilateral salpingectomy in preventing ovarian cancer. More awareness is needed in clinicians and the public about the benefit of bilateral salpingectomy during a gynecological surgery for a benign reason in high-risk patients, such as those who has a family history of ovarian cancer, BRCA carriers who deny for BSO, and those who want permanent contraception. In the future, better research design is needed to show the long-term effect of bilateral salpingectomy on preventing ovarian cancer, as well as preserving ovarian function.

Table 1. Summary of studies based on clinicians' views on BS

References	Year	Region	Clinicians who responded the survey (n)	Clinicians incorporated BS (%)	BS performed to reduce risk of ovarian cancer (%)	Clinicians refusing to conduct BS (%)	Reasons for refusal to perform BS
Gill <i>et al</i> ⁴⁰	2013	US	234	54.3	75	45.5	69.4%-no benefit
Reade <i>et al</i> ⁴¹	2013	Canada	192	45	90	55	51%-no benefit
Kapurubandars <i>et al</i> ⁴²	2015	Australia	382	70	90	30	36%-insufficient evidence to show benefit
Venturella <i>et al</i> ⁴³	2016	Italy	479	81.97	88	18.03	54.65%-no benefit
Garcia <i>et al</i> ⁴⁴	2016	US	249	86	NA	14	36%-difficulty in accessing fallopian tube

BS: bilateral salpingectomy; NA: not available.

Conflict of Interest Statement

All authors have no conflict of interests to disclose.

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