

Review

Ovarian Function in Patients Who Underwent Opportunistic Bilateral Salpingectomy during Hysterectomy

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Abstract

Objective(s): To provide additional data and to inform all women at average risk of ovarian cancer, undergoing a benign gynecological laparoscopic procedure about the Pro's and the Con's of opportunistic bilateral salpingectomy (OBS). **Mechanism:** Risk reducing salpingo-oophorectomy to prevent epithelial ovarian cancer (EOC) is associated with decreased quality of life and increased overall mortality. OBS has emerged as a primary prevention of ovarian cancer through a paradigm shift in which fallopian tubes are often the cause of ovarian cancer rather than the ovaries themselves. **Findings in Brief:** Causal relationship of salpingectomy and reduced risk of ovarian cancer has not been proven yet. There are several population-based studies that showed bilateral salpingectomy reduced risk of EOC by 42–67%, but there also is a study that suggest increased risk of ovarian cancer after salpingectomy. As for risk of surgical complications, several cohort studies have demonstrated that there was no increase in rates of hospital readmission, blood transfusion, day of hospital stay. However, recent meta-analysis stated that there were insufficient data to assess any difference in both intraoperative and postoperative complication rates. The procedure of salpingectomy can disrupt blood supply to the ovary. Data of reproductive outcome after assisted reproductive technologies such as in vitro fertilization and embryo transfer (IVF-ET) are conflicting. Some studies suggest that salpingectomy did not compromise the outcome of IVF-ET, but other studies found that salpingectomy may lead to decreased ovarian reserve after salpingectomy. For patients who do not wish fertility, data on the effect of OBS during hysterectomy suggest that changes in serum ovarian reserve markers were not different between OBS group and control group. **Conclusions:** Bilateral salpingectomy should be considered at the time of abdominal or pelvic for women at average risk of ovarian cancer. However, physicians should discuss the protective benefit of bilateral salpingectomy against ovarian cancer and controversial data on ovarian reserve.

Keywords: epithelial ovarian cancer; opportunistic bilateral salpingectomy

1. Introduction

Epithelial ovarian cancer (EOA), which accounts for more than 85% of all ovarian cancers is most lethal gynecological malignancy [1]. Because screening method for ovarian cancer such as Transvaginal ultrasonography, and tumor markers and even liquid biopsies in a recent study, has limited value in detecting early stage EOA, EOA was usually detected in the advanced stage [2,3]. Despite the standard treatment of cytoreductive surgery and combination chemotherapy with recent development of targeted anti-cancer and/or immune-oncologic agents, survival after the diagnosis of ovarian cancer had little improvement over time [4]. Some studies even showed that these method in hope of early detection of ovarian cancer led to increased rate of unnecessary surgery or complications caused by surgery [5–7]. Therefore, with failure to find innovative therapeutic or early detecting modalities, attention has

shifted to the prophylactic method to prevent ovarian EOA [8].

Patients with germline mutations in the BRCA1 and BRCA2 genes are exposed to higher chance of breast cancer and EOA. Approximately 9–24% of EOA are due to germline mutations in BRCA1 and BRCA2, and patients with BRCA1 or BRCA 2 mutation have approximately 39–46% and 10–27% risk of ovarian cancer by age of 70 year, respectively [9,10]. Some experts suggested that routine ovarian cancer screening either by ultrasonography or serum CA 125 measurement is not recommended because they have not been proven to decrease the mortality rate in this population as well [11,12]. The most effective ovarian cancer risk reduction strategy for these patients with increased risk of EOA is risk-reducing bilateral salpingo-oophorectomy [11]. However, even though risk-reducing bilateral salpingo-oophorectomy is associated with 75–96%



decrease in ovarian cancer risk in BRCA mutation carriers, the procedure result in surgical menopause, which can lead to detrimental effect on cardiovascular health, osteoporotic health and decreased quality of life due to perimenopausal symptoms such as hot flashes [13–15]. Moreover, in general population with average risk of ovarian cancer, bilateral oophorectomy before menopause is associated with increased overall mortality [15,16], which makes it inapplicable method to prevent EOA in women with average risk of ovarian cancer.

2. Proposed Mechanism of Opportunistic Bilateral Salpingectomy

Opportunistic bilateral salpingectomy (OBS) has emerged as a mean of preventing EOA without surgical menopause after the paradigm of epithelial ovarian carcinogenesis has shifted [4,17–19]. Traditionally, remodeling of ovarian surface epithelium after ovulation had been accepted as the cause of malignant transformation of ovarian cells [20–22]. After histologic examination of ovaries and tubes from patients who carry BRCA mutations, data have shown that 5–9% have cancer or precursor lesions, 70–100% of which are in the tube, not ovaries [23,24]. Molecular studies also showed that these serous tubal intraepithelial carcinomas closely resembles ovarian high-grade serous carcinomas, and express TP53 mutation, which is common in high-grade serous carcinomas of ovary [25,26]. Conversely, gene expression of high-grade serous carcinomas express a müllerian marker PAX8 which is more related to fallopian tube, and not calretinin which is a mesothelial marker that is related to ovarian surface epithelium [27]. This concept that EOA are derived from the fallopian tube have given rationale for performing prophylactic salpingectomy rather than salpingo-oophorectomy to prevent ovarian cancer.

3. Current Guidelines on Opportunistic Bilateral Salpingectomy

In 2013, Society of gynecologic oncology stated that OBS may be appropriate and feasible as a strategy for EOA risk reduction [19]. This statement recommends discussion of risk-reducing salpingectomy with women in average risk of ovarian cancer at the time of abdominal or pelvic surgery, hysterectomy or in lieu of tubal ligation.

In compliance of this statement, many national societies have published a statement regarding OBS [28]. In 2018, Korean society of obstetrics and gynecology published a position statement that women at average risk of EOA who planned to undergo hysterectomy for benign gynecologic disease should be counseled regarding salpingectomy at the time of hysterectomy [29]. The statement recommends to give patient enough information on benefits of salpingectomy such as possible reduction of ovarian/fallopian/peritoneal cancer, minimal potential of decreased ovarian reserve.

American college of obstetricians and gynecologists also published a committee opinion on OBS to prevent EOA in 2019 [4]. They concluded that salpingectomy at the time of hysterectomy or for sterilization appears to be safe and the surgeon and patient should discuss the potential benefits of reducing EOA and the risks and benefits of alternative procedures such as bilateral salpingo-oophorectomy.

4. Efficacy of Opportunistic Salpingectomy on Reduction of Epithelial Ovarian Cancer

Data have already shown that tubal ligation led to decreased risk of EOA [30–32]. A meta-analysis published in 2011 which included 19 cohort studies showed that the risk of EOA was reduced by 34% after tubal ligation [33]. More recent meta-analysis in 2012 included 30 case control studies or cohort studies and concluded that the relative risk for EOA for patients with tubal ligation was 0.70 (95% CI: 0.64–0.75) [34].

Causal relationship of salpingectomy and reduced risk of ovarian cancer has not been proven yet because the prospective data showing the risk of ovarian cancer later in life in patients who underwent opportunistic salpingectomy is lacking. There are a few population-based studies that shows close relationship between the history of salpingectomy and the risk of EOA. In 2015, a nationwide register-based case control study in Denmark showed a reduced risk of epithelial ovarian cancer by 42% (OR: 0.58, 95% CI 0.36–0.95) in patients with bilateral salpingectomy [35]. In the same year, a population-based study in Sweden showed a significantly lower risk of ovarian cancer among women with any types of previous salpingectomy (HR: 0.65, 95% CI: 0.52–0.81), and a 50% decrease in risk in patients with a history of bilateral salpingectomy compared to unilateral salpingectomy (HR: 0.35, 95% CI: 0.17–0.73, and HR: 0.71, 95% CI: 0.56–0.91, respectively) [36]. A nationwide population-based study using Dutch pathology database also showed that bilateral salpingectomy resulted in decreased incidence of EOA (HR: 0.43, 95% CI: 0.06–3.16) [37]. However, the population-based study in Taiwan reported against results of effect on salpingectomy in EOA. The study revealed that the gynecological surgeries including salpingectomy increased the risk of ovarian cancer (hysterectomy with salpingectomy vs hysterectomy vs salpingectomy vs control: 52.5 vs 45.5 vs 23.3 vs 9.43 per 10 person-years, respectively) [38].

These population-based cohort studies are not conclusive to prove causal relationship between salpingectomy and the risk of ovarian cancer so far. Despite large size of study population, they included relatively small number of women who underwent bilateral salpingectomy, and possible confounding factors such as reasons for salpingectomy or the various histologic type of EOA were not adjusted for most studies. Thus, further prospective data are needed to confirm the possible role of OBS on risk reduction of EOA.

5. Concerns about Opportunistic Bilateral Salpingectomy

5.1 Risk of Cancer Development

Even though it is widely accepted that EOC origin from tubal lesions such as tubal intraepithelial carcinomas, data shows that only 40 to 60% of ovarian high-grade serous carcinomas develop in fallopian tubes [24,39]. Suggested mechanisms for non-tubal origin of EOC include malignant transformation of ovarian cortical inclusion glands or rare serous borderline tumor [40], both of which cannot be prevented by OBS. Furthermore, estrogen produced by remaining ovaries can affect the risk of breast cancer development [41]. Recent meta-analysis reported that the risk of breast cancer was reduced after risk-reducing bilateral salpingo-oophorectomy in patients with germ line BRCA mutation [42]. In patients who have undergone bilateral salpingo-oophorectomy, hormone replacement therapy has been reported to increase the risk of breast cancer [43]. Therefore, there are still risks of developing estrogen dependent tumors such as breast cancer and EOC in patients after OBS.

5.2 Safety

Because salpingectomy involves steps of separating fallopian tube from adjacent ovary and coagulation of blood supply to the fallopian tube, there is a concern that addition of salpingectomy may lead to increased risk of surgical complications. Several cohort studies have demonstrated that there was no increase in rates of hospital readmission, blood transfusion, day of hospital stay between patients who underwent OBS during hysterectomy [44–48]. Surgical complications intraoperatively (bleeding, bladder injury or ureteral injury) or postoperatively (fever, infection or vaginal cuff dehiscence) were not shown to be increased after OBS as well [48,49]. However, a meta-analysis including 7 randomized controlled trials stated that there were insufficient data to assess any difference in both intraoperative and short-term postoperative complication rates because the number of events were too low (intraoperative complication: 2/145 vs 3/141, short-term postoperative complication: 0/78 vs 2/74) [50].

5.3 Reproductive Outcome of Assisted Reproductive Technologies after Salpingectomy

Anatomically, fallopian tube is closely related to the ipsilateral ovary. The procedure of salpingectomy can directly damage ovarian vessel or disrupt the collateral blood supply to the ovary in the mesosalpinx. These damages can be done by excision itself or thermal spread during electrocautery.

Data of reproductive outcome after assisted reproductive technologies such as in vitro fertilization and embryo transfer (IVF-ET) are conflicting. In a prospective cohort study in 2013 on 134 IVF-ET cycle in patients with tubal factor infertility showed that bilateral salpingectomy resulted in higher implantation rate (51% vs 30.4%) with

comparable AMH, AFC and number of retrieved oocyte [51]. Clinical pregnancy rate and live birth rate showed a higher trend in bilateral salpingectomy without statistical significance. Likewise, a retrospective study in 2013 on 288 fresh IVF-ET cycles in tubal factor infertility women showed that the rate of implantation, clinical pregnancy and live birth were similar between salpingectomy group and the control group [52]. Moreover, in women with unilateral salpingectomy, mean number of follicles and retrieved oocytes on ipsilateral ovary of operated salpinx were similar to those from the contralateral ovary. A meta-analysis published in 2019 that included 7 studies on salpingectomy due to ectopic pregnancy concluded that salpingectomy do not exert negative effect on ovarian reserve or ovarian response after gonadotropin stimulation [53].

On the contrary, some studies found that salpingectomy may lead to decreased ovarian reserve after salpingectomy. Grynnerup *et al.* [54] showed decreased AMH in 16 women with salpingectomy compared to 42 women with tubal factor infertility without salpingectomy (median 16.1 vs 23.4 pmol/L, $p = 0.04$). A retrospective study also showed that mean patients with bilateral salpingectomy showed significantly low level of AMH (183.48 vs 127.11 fmol/mL; $p \leq 0.037$) and higher level of FSH in early follicular phase (7.85 vs 9.13 mIU/mL; $p = 0.048$), even though number of retrieved oocytes or viable embryos were similar [55]. A meta-analysis including 13 (4 randomized controlled studies, 12 cohort studies) was published in 2016, and concluded that salpingectomy was associated with lower level of AMH and higher level of follicle stimulating hormone, but the number of collected oocytes and clinical pregnancy rates were not altered [56]. A randomized controlled study in 2019 compared salpingectomy with proximal tubal occlusion in patients with hydrosalpinx [57]. Salpingectomy resulted in not only decreased AMH (AMH; 3.7 ng/mL vs 2.6 ng/mL; $p < 0.001$) and AFC (AFC; 10.6 vs 8.6; $p < 0.001$), but also lower fertilization rate and number of grade 1 embryos.

5.4 Ovarian Function after Opportunistic Bilateral Salpingectomy during Hysterectomy

The effect of OBS during hysterectomy on ovarian reserve has been reported by several randomized controlled trials. Changes in serum AMH level in patients with hysterectomy was shown to be unaffected by salpingectomy after 3 months [45,58,59] or 6 months [60] postoperatively. Changes in serum FSH levels were also not different between salpingectomy group and control group after 3 months [45,61] or 6 months [62]. Changes in other markers of ovarian reserve such as antral follicle count, mean ovarian diameter and peak systolic velocity were not significantly altered due to salpingectomy [45]. Based on these results, a meta-analysis published in 2019 showed that postoperative hormonal status was compatible with no difference in patients with salpingectomy compared to those

without salpingectomy [50]. Studies published after 2019 also confirmed that ovarian reserve was not significantly compromised by adding salpingectomy during hysterectomy after 3 months [63,64] and 9 months [64]. As for long term outcome, an observational study of previous randomized controlled trial [45] showed that addition of prophylactic bilateral salpingectomy to total laparoscopic hysterectomy did not modify ovarian age calculated based on AMH, FSH, antral follicle count, vascular index, flow index and vascular flow index up to 3 to 5 years.

6. Conclusions

Bilateral salpingectomy should be considered at the time of abdominal or pelvic surgery or in lieu of tubal ligation even for women at average risk of ovarian cancer. However, because the reproductive outcome of assisted reproductive technologies such as IVF-ET after bilateral salpingectomy are debatable so far, physicians should discuss the protective benefit of bilateral salpingectomy against ovarian cancer and controversial reproductive outcomes after assisted reproductive technology. For women at average ovarian cancer risk, OBS during hysterectomy due to benign gynecologic conditions seems to be feasible method to prevent ovarian cancer. Even though current data do not strongly suggest the decrease in ovarian reserve after OBS during hysterectomy, more large scale randomized controlled trials on long term effect of OBS on ovarian reserve are needed to confirm these results.

Author Contributions

MP and HJY conceptualized the manuscript. SYS, YWJ and JHM analyzed and interpreted the data, and wrote the draft. SYS, YWJ, JHM, WKS, MP and HJY all contributed majorly in writing, revision and approval of the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest. HJY is serving as one of the Editorial Board members/Guest editors of this journal. We declare that HJY had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to MHD.

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