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Review Article

The Role of Opportunistic Bilateral Salpingectomy vs Tubal Occlusion or Ligation for Ovarian Cancer Prophylaxis

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ABSTRACT Bilateral tubal ligation (BTL) for sterilization has been known to decrease the risk of ovarian cancer. Recent studies have suggested that bilateral salpingectomy (BS) may be an alternative to BTL or tubal occlusion for women desiring permanent sterilization, owing to a possibly greater protective effect against ovarian cancer. We conducted a PubMed/MEDLINE review of the literature for original studies, opinion articles, and meta-analyses published between 2010 and 2016 addressing the role of BS at the time of sterilization and comparing its efficacy with BTL in terms of ovarian cancer prevention, operative outcomes, and ovarian function. BTL has been found to decrease the risk of any ovarian cancer by 13% to 41%, compared with 42% to 78% for BS. Although operative time is increased with BS compared with BTL, no differences in complication rates or ovarian reserve between the 2 procedures have been demonstrated. Our review suggests that BS should be discussed when BTL is being considered, and that patients should be counseled about the risks and benefits of both procedures based on the current available evidence. Journal of Minimally Invasive Gynecology (2017) 24, 371–378 © 2017 AAGL. All rights reserved.

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Ovarian cancer is the fifth-leading cause of death among women in the United States with the highest mortality rate of gynecologic malignancies [1]. Current evidence suggests that the origin of ovarian cancer, particularly the high-grade serous epithelial subtype, arises from a primary site within the fallopian tubes before metastasizing to the ovaries [2–4]. The inverse relationship between bilateral tubal ligation (BTL) and the incidence of ovarian cancer has been well documented [5,6]. This evidence has led to an increase in the use of opportunistic bilateral salpingectomy (BS) at the time of hysterectomy and sterilization. It has become increasingly common practice to counsel patients on BS at the time of permanent sterilization as a prophylactic measure against future ovarian cancer [7,8]. In the setting of salpingectomy as an alternative to BTL, questions that arise in addition to establishing the effectiveness of ovarian cancer prevention are its implications in terms of surgical outcomes, ovarian reserve, and effectiveness in pregnancy prevention; however, available data are limited.

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Ovarian Cancer and Its Origin

Ovarian cancer is the seventh most common cancer in women worldwide [9], causing 3.6% of all cancers in females and affecting approximately 230,000 women annually. Between 90% and 95% of ovarian cancers are epithelial carcinomas [10], and these can be further subdivided into the following major histological subtypes: high-grade serous (70%–80%), mucinous (3%), endometrioid (10%), clear cell (10%), and low-grade serous (<5%) [11,12].

Multiple theories exist regarding the original malignant transformation from which ovarian cancer arises. In women with known genetic predisposition, such as the *BRCA1/2* gene, the responsible tumor-suppressor gene mutation has been recognized, predisposing breast and ovarian tissues to DNA aberrations. The generally accepted theory for initiation of non-*BRCA* ovarian cancer is that regular ovulation exposes the ovarian surface epithelium to excess opportunities for malignant transformation, also known as the "incessant ovulation theory" [13,14]. Some researchers theorize that ovarian surface endothelium is predisposed to malignant change secondary to endometriotic implants or inclusion cysts; another theory is that recurrent pelvic inflammation causes undue oxidative stress and cellular pathway alterations [15–18].

Recent large studies have provided significant evidence suggesting the fallopian tubes as the site of initial malignancy in a large proportion of ovarian cancers. As early as 1896, Doran suggested the fallopian tube as a likely site of serous carcinoma [19]. In a study reported by Piek et al [20] in 2001, early cellular abnormalities were found in the fallopian tubes of women with known *BRCA* mutation who underwent a prophylactic bilateral salpingo-oophorectomy (BSO) [20], prompting closer examination of the fallopian tubes in women undergoing prophylactic surgery and in women with sporadic pelvic cancers. Occult fallopian tube malignancy has since been identified in up to 9% of patients with *BRCA* mutation undergoing prophylactic surgery [21–23], and in up to 60% of patients with sporadic pelvic high-grade serous carcinoma [24–26].

In 2006, Lee et al [27] identified the "p53 signature," an alteration in the immunostaining of p53 tumor-suppressor proteins within the fallopian tubes. Aberrations in the p53 tumor-suppressor pathway have long been closely associated with high-grade serous ovarian carcinomas (HGSOCs), and in many cases such an aberration is considered the inciting event leading to carcinoma [28–30]. These p53 signatures are common within nonneoplastic fallopian tubes, but are significantly more frequent in association with tubal intraepithelial carcinomas (TICs), suggesting a candidate pathway for pelvic serous cancers [27]. The p53 signature is now considered a potential precursor lesion for high-grade serous carcinomas of the fallopian tubes [31–34]. In 2007, Kindelberger et al [24] demonstrated that many ovarian serous tumors share identical p53 mutations as coincident TICs and p53 signatures. Kuhn et al [35] performed a mutational analysis of 29 cases of high-grade serous carcinoma with concurrent TICs and identified identical p53 mutations in 27 of 29 pairs, suggesting a clonal relationship between the 2 tumor types [35]. Interestingly, p53 signatures have rarely been identified within the ovarian surface epithelium, suggesting a tubal origin to both p53 signatures and HGSOCs [36].

More recent studies examining the genotype and gene expression profiles of HGSOCs have noted a closer resemblance to the fallopian tube compared with the ovarian surface epithelium [37,38]. Manipulation of human fallopian tubal epithelial cells in vitro and in xenograft mouse models have demonstrated transformation into tumors that histologically and genetically mimic HGSOCs [39–41]. Further studies have supported the hypothesis of an initial tubal malignancy and have to suggested a fimbrial-ovarian etiology of ovarian cancer [27,42–44]. TICs appear to be associated specifically with the development of serous subtype epithelial ovarian cancer (EOC) [2,44]. Risk-reducing prophylactic BSO is already a well-accepted practice in women with known *BRCA* mutation [45], and with new evidence suggesting fallopian tubes as a possible precursor site for ovarian cancer, many physicians are now suggesting BS in lieu of BTL as a method of sterilization based on its additional advantage of ovarian cancer prophylaxis.

Risk of Ovarian Cancer After Bilateral Tubal Ligation

Early evidence has shown that women who undergo BTL for elective sterilization have an overall decreased rate of ovarian cancer. Although the protective effect of tubal ligation is well accepted, the underlying mechanism for this effect is not yet understood. In addition, studies examining risks stratified by histological subtype have been limited to date.

We conducted a literature search of the PubMed/MEDLINE databases for all original studies, opinion articles, and meta-analyses with the key phrases "ovarian cancer" and "tubal ligation" in the title published since 2010. Inclusion criteria required that articles address the incidence of ovarian cancer, but did not require analysis of histological subtype. Six original research publications [46–51] and 3 meta-analyses [52–54] were identified (Table 1).

In 2011, Cibula et al [52] conducted a meta-analysis of 32 studies published from 1989 to 2007 and concluded that compared with women who received no intervention, women who had undergone BTL had a relative risk (RR) of 0.66 (95% confidence interval [CI], 0.60–0.73) for EOC and an, RR of 0.68 (95% CI, 0.61–0.75) for invasive ovarian cancer. They further analyzed subtypes and reported an RR of 0.73 (95% CI, 0.63–0.85) for serous invasive cancer and an RR of 0.40 (95% CI, 0.3–0.53) for endometrioid invasive cancer. Although the reported RRs for borderline tumors (0.86; 95% CI, 0.67–1.10) and mucinous ovarian cancers (0.82; 95% CI, 0.54–1.27) were lower, the differences were not statistically significant.

In 2012, Rice et al [53] published a meta-analysis of 30 studies from 1969 to 2011, which showed similar results. In women who underwent BTL, the RR for all ovarian cancers was 0.70 (95% CI, 0.64–0.75). By subtype, the RR was 0.75 (95% CI, 0.65–0.88) for serous cancers, 0.45 (95% CI, 0.33–0.61) for endometrioid cancers, 0.88 (95% CI, 0.70–1.09) for mucinous cancers, and 0.72 (95% CI, 0.55–0.94) for clear cell ovarian cancer.

In 2013, Sieh et al [54] performed a more specific meta-analysis of 13 case-control studies and reported similar findings. Women who had undergone BTL had an odds ratio (OR) of 0.81 (95% CI, 0.74-0.89) for developing any invasive serous cancer, an OR of 0.48 (95% CI, 0.40-0.59) for developing endometrioid cancers, an OR of 0.52 (95% CI, 0.40-0.67) for developing clear cell ovarian cancer, and an OR of 0.68 (95% CI, 0.52-0.89) for developing mucinous cancers.

These meta-analyses arrived at the same conclusion, that there is a protective effect from BTL on ovarian cancer, with a greater protective effect on endometrioid invasive cancers compared with serous invasive cancer and a less well-defined effect for clear cell and mucinous cancers. Rice et al [47] continued their investigation with 2 original analyses. In 2013, they published results from data collected during a large case-control study conducted from 1978 to 2008,