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Mini Review

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The Opportunistic Salpingectomy in Reducing Ovarian Cancer Risk: Do the Potential Benefits Outweigh Complications?

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ABSTRACT

A 33-year-old women with 3 children who has completed child bearing presents to your office for permanent sterilization *via* a laparoscopic approach. She has recently heard through the internet that removal of the fallopian tubes completely may decrease her ovarian cancer risk more than a tubal ligation with placement of clips or cauterization. She has no family history of gynecologic malignancies but is now curious about preventative measures for ovarian cancer that can decrease her risk. How do you counsel this patient?

KEYWORDS: Cancer; Fallopian tubes; Gynecologic malignancies; Tumors.

ABBREVIATIONS: BRCA 1 or BRCA 2: BReast CAncer genes 1 or 2; ACOG: American College of Obstetricians and Gynecologists; EOC: Epithelial Ovarian Cancer; PPC: Primary Peritoneal Cancer; BSO: Bilateral Salpingo-Oophorectomy; BTIs: Biliary Tract Infections; BS: Bilateral Salpingectomy; RCT: Randomized Control Trials.

INTRODUCTION

Ovarian cancer is the leading cause of gynecologic malignancies in the United States and the 5th most common cause of cancer deaths in women.[1,2] Screening methods have shown no mortality benefits, and symptoms are non-specific leading to delays in diagnosis. The most common form of ovarian cancer is epithelial carcinoma, with stromal/sex cord tumors and germ cell tumors much less common. The most common types of epithelial ovarian cancer, in decreasing order, are serous (50%), mucinous (25%), endometrioid (15%), clear cell, and transitional or Brenner tumor. The diagnosis of ovarian cancer is often in late stages, leading to a five-year survival rate of less than 50%.[2] While the risk of ovarian cancer in genetically predisposed patients with (BReast CAncer genes 1 or 2) BRCA 1 or BRCA 2 mutations ranges from 20-50%, the risk for the general population remains at less than 2%.[2] Many genetically predisposed women may decide to undergo prophylactic surgeries to decrease their risk of developing ovarian cancer and face the consequence of surgical premature ovarian failure.

The fallopian tubes, specifically the fimbriae, have been suggested as possible originating sites of epithelial ovarian cancers.[3] Historically, cancer of the fallopian tubes had been the least common gynecologic malignancy (0.3%). Zweemer et al's[4] findings suggested an increased incidence of fallopian tube cancer in patients harboring a BRCA 1 mutation and suggested that carriers undergoing prophylactic oophorectomy may benefit from considering salpingectomy as well. Peritoneal washings performed at the time of surgery have found unsuspected fallopian tube carcinoma.[5,6] These early diagnoses made it possible to identify fallopian tube carcinoma before significant spread to the ovary, which makes differentiation more difficult and likely leads to under-reporting of primary tubal carcinoma. Additionally, fallopian tube sectioning at the time of salpingo-oophorectomy for serous carcinoma has shown tubal involve-

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ment in a significant portion, particularly the distal tube and fimbriae.[7] Bilateral tubal interruptions have been shown to have a negative association with epithelial ovarian cancer. Several possible mechanisms have been proposed, with the most common being an interruption in retrograde migration of epithelial tissue from the uterus to the ovaries.[8-10]

These recent findings that a proportion of ovarian carcinomas may originate in the fallopian tubes have led to the consideration of excisional sterilization techniques (salpingectomy), rather than non-excisional (clips, cauterization), to further decrease this risk. Also consideration for concurrent salpingectomy during a hysterectomy for benign reasons (e. g., menorrhagia, uterine leiomyomas)

Proposals for prophylactic surgeries were first made in BRCA positive patients. Surgeries included bilateral salpingo-oophorectomy as well as bilateral salpingectomy and delayed oophorectomy. There is less literature on the benefits of these prophylactic surgeries in BRCA negative patients.

This review will present the current literature on salpingectomy as a means of risk reduction of epithelial ovarian carcinoma including the potential drawbacks, the benefits, and the current physician adoption of salpingectomy as a means of sterilization.

POTENTIAL BENEFITS

The American College of Obstetricians and Gynecologists (ACOG) released their committee opinion in January 2015 suggesting salpingectomy as an option to be discussed with patients for sterilization and as having potential for ovarian cancer prevention. This recommendation is also extended to women undergoing hysterectomy procedures.

There have been several studies examining the absolute decrease risk of ovarian cancers in healthy women undergoing tubal ligations procedures including non-excisional procedures; tubal ligation alone appears to decrease risk of ovarian cancers. Sieh et al[9] pooled primary data from 13 population based case control studies in various countries including the US, Germany, Denmark, Australia, and Canada. These included 13,904 controls, 7942 invasive ovarian cancer cases, and 2215 borderline ovarian tumors and assessed whether the women had surgical history of a non-excisional (cauterization, clips) tubal ligation. They found a 29% reduced risk of invasive ovarian cancer overall after accounting for numerous confounders. Reduced risks were consistently found for every site and across 4 histologic subtypes: endometrioid, clear cell, mucinous and serous high grade ovarian. This study did not include excisional tubal procedures.

Madsen et al[11] performed a case control study of the entire female Danish population that included all women in Denmark diagnosed with epithelial ovarian carcinoma or borderline carcinoma between 1982 and 2011. Tubal ligation alone was associated with a statistically significant decreased risk of ovarian carcinoma, highest for endometrioid tumors (odds ratio (OR)=0.87; 95% confidence interval (CI) 0.78-0.98). Bilateral salpingectomy was associated with an overall 42% decreased risk of epithelial ovarian carcinoma (OR=0.58; 95% CI 0.36-0.95). Benefits of this study included histologic verification of tissue, use of national registry to eliminate recall and selection bias, and population size (13,241 cases with epithelial ovarian cancer (EOC) and 3,605 with borderline ovarian tumors matched with randomly selected 15 female population controls).

Similar were found in a nested case control study using Rochester Epidemiology Project data between 1966 and 2009.[12] One hundred and ninety-four cases of serous EOC and primary peritoneal cancer (PPC) were matched with 388 controls. Any type of tubal sterilization procedure conferred a 46% decrease risk of serous EOC and PPC (OR, 0.54; 95% CI 0.28-1.04; p=0.07). There was a 64% risk reduction among excisional techniques compared to no sterilization and non-excisional techniques combined, however once other factors such as OCP use, pregnancy, and live births were adjusted for (as these were more common in non-excisional techniques) this decreased to 23% risk reduction, which was no longer statistically significant. Limitations encountered were missing operative reports and low statistical power due to a small amount of cases.

Falconer et al[13] in 2015 utilized a large population based cohort study from 1973-2009 on the general population in Sweden with the primary outcome of ovarian and tubal cancer, excluding borderline carcinomas as these have been shown as stated above to not be associated with bilateral tubal interruption (BTIs). Researchers compared outcomes in women who had undergone hysterectomy (98,026), hysterectomy+bilateral salpingo-oophorectomy (BSO) (37,348), salpingectomy (34,433), and non-excisional sterilization (81,658). Mean age at entry was 35.9 years and mean follow-up was 23.1 years. Women were excluded if they had had any gynecologic surgical procedure prior to entering the cohort. Three-thousand and fifty-one women were identified as having two-sided salpingectomies and 19,552 as having one-sided salpingectomies. Both unilateral and bilateral salpingectomies were associated with statistically significant risk reductions, however bilateral salpingectomy was associated with an additional 50% decrease compared with a unilateral procedure. Number needed to treat for bilateral salpingectomy group was about 300 women, which is expected for a cancer with lower incidence. Statistically significant results were only observed at least 10 years out from surgery in all groups except for the hysterectomy group. This suggests a true association as opposed to a "healthy screenee effect".

Level one evidence with randomized control trials have not been performed as of this time, there is a consistent risk reduction for ovarian cancers after bilateral salpingectomy (performed for sterilization and concurrent with a hysterectomy) in cohort studies and retrospective analyses.

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POTENTIAL HARMS

Several potential complications have been hypothesized including increased length of surgery and complication rates, increased length of hospitalization and readmission, necessity of blood transfusion, and increased cost.

Early studies have brought to light the potential complications that salpingectomy may have on patients, both during and after the procedure. The large retrospective cohort study by McAlpine et al[14] brought to light several peri-operative differences in procedures with and without salpingectomy. The mean difference in operating time was found to be statistically significantly longer among hysterectomies with bilateral salpingectomy when compared to hysterectomy alone (16 minutes; $p<.001$). Patients who underwent hysterectomy alone were found to actually have slightly longer length of stay compared to patients who underwent hysterectomy+bilateral salpingectomy (2.52 days *vs.* 2.37 days; $p=.010$). Hospital readmission and need for blood transfusion was not significantly different between hysterectomy alone group and hysterectomy+salpingectomy.

For patients who underwent salpingectomy for sterilization compared with tubal ligation, mean OR time was increased significantly by 10.2 minutes ($p<.001$).[14] There were no significant differences found for length of stay, readmission, or blood transfusion.

Many of the women in the general population that may undergo prophylactic salpingectomy are premenopausal, therefore, ovarian function post-procedure is an important factor to take into consideration. Preliminary studies have found no significant differences in ovarian function by measuring changes in anti-mullerian hormone levels, follicle stimulating hormone levels, change in antral follicle number, change in mean ovarian diameter, and change in peak systolic velocity.[15,16] Salpingectomy did not significantly affect ovarian function based on the above measurements.

Another concern about performing salpingectomy as sterilization or as part of a concurrent procedure with hysterectomy has also been cost. Cost analysis was assessed using a Monte Carlo simulation model comparing opportunistic salpingectomies to non-excisional tubal ligations, as well as comparing hysterectomies alone, with combined bilateral salpingectomy (BS) or combined bilateral salpingo-oophorectomy (BSO).[17] When comparing salpingectomy to non-excisional tubal ligation, it was found to be cost effective for reducing the risk of ovarian carcinoma so long as the cost of salpingectomy does not exceed that for a tubal ligation by more than $1000. The simulator found that taking into account all costs, hysterectomy combined with bilateral salpingectomy was more cost effective than either hysterectomy alone and hysterectomy+BSO. Compared with hysterectomy+BSO, hysterectomy+BS was less effective at preventing ovarian cancer as would be expected, but conferred more risk reduction than hysterectomy alone. Most importantly, bilateral salpingectomy did not increase the risk of other cancers (lung, colorectal) and cardiovascular disease as a BSO. The number needed to treat with an opportunistic salpingectomy to prevent one case of ovarian cancer was 273-366. The high number needed to treat offsets the apparent gain in life expectancy for women affected by ovarian carcinoma that could have been prevented by an opportunistic salpingectomy.

Although surgical time appears to be increased in these retrospective studies, complication rates appear to be low for salpingectomy without increasing overall costs.

CONCLUSIONS

The recent findings of the benefits along with the low risk profile associated with salpingectomies have led to a steady increase in salpingectomies. In addition to evaluating risks and complications of the procedure, McAlpine et al[11] also evaluated procedural uptake after a 2010 educational initiative in British Columbia. The most striking evidence was the statistically significant increase in salpingectomy specifically for sterilization. Combined hysterectomy+salpingectomy also significantly increased.

Randomized control trials (RCT) are still lacking, especially among women with general population risk. Findings thus far have found repeated associations between tubal procedures and serous, endometrioid, and clear cell epithelial carcinomas, and very few potential risks have been associated with salpingectomy, including increased surgical risks and decreased ovarian reserve.

It is well known that ovarian cancer is the leading cause of gynecologic malignancy death, the fifth leading cause of cancer death in women, and that screening programs have had little success. The current literature, although limited, has shown that non-excisional tubal sterilization procedures are associated with decreased ovarian cancer rates, with excisional procedures reducing the risk further, and these results have been replicated. Although level-one evidence is lacking and ACOG is unable to make an absolute recommendation for women with general population risk, shared patient-physician decision-making is most acceptable. The potential benefits are promising, and risks appear to be low; therefore bilateral salpingectomy can be recommended and encouraged in low-risk women presenting for permanent sterilization as well as those undergoing hysterectomy for benign reasons.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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