Editorial

Remove the Fallopian Tubes and save the Ovaries: The Emergence of Opportunistic Salpingectomy to reduce Ovarian Cancer Risk

Ovarian cancer is the 7th most common cancer and the 5th most common cause of cancer deaths in women. It is the 2nd most common gynecologic cancer and the most common cause of death from gynecologic cancer. Epithelial ovarian cancer accounts for over 90% of ovarian cancers. Its histologic subtype 'high-grade serous' (70%) mostly presents in advanced stages (III or IV) and has a poor prognosis. Other histologic subtypes are low-grade serous (4%), endometrioid (10%), clear cell (10%) and mucinous (4%). Despite exciting innovations in surgical technique and chemotherapy, including targeted therapy and antiangiogenic agents, the overall survival rate has not improved over 4 decades.

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Mortality from ovarian cancer is low if it is diagnosed in an early stage when the 5 year survival rate is 80 to 90%, which drops to 19 to 32% in advanced disease. There is no reliable screening test or method for its detection in an early stage and 70 to 80% of the women are diagnosed in advanced stages. Even in advanced stages, an earlier detection can reduce mortality as the tumor volume may be less and optimal cytoreduction may be achieved at surgery. Cure rates are higher with optimal cytoreduction (<1 cm of residual disease) than with suboptimal (30-40% cure *vs* 15-20%) and the most significant factor associated with optimal cytoreduction is the volume of disease.

To reduce the impact of ovarian cancer on women's health, we need to detect it in an early stage and also prevent it from occurring. Options to detect it early (and aim for a cure) include periodic clinical examination, transvaginal sonography and estimation of serum CA-125 level, but these have not been found to be uniformly effective. Ovarian cancer has been called a 'silent abdominal tumor' because symptoms occur late in the course of the disease. These symptoms are abdominal distension, nausea and early satiety due to the presence of ascites, and peritoneal/omental metastases. However, some symptoms are reported by women even at early stages. Abdominal or pelvic pain, bloating, difficulty in eating or feeling full and urinary urgency or frequency need to be evaluated especially if they are of recent onset, occur repetitively and are persistent rather than fluctuating.

Currently, strategies to prevent ovarian cancer are targeted toward women at an increased risk due to family history and gene mutation. Risk-reducing bilateral salpingo-oophorectomy (BSO) is reserved for women at the highest risk. Women with a breast cancer 1 (BRCA1) gene mutation have a 35 to 46% lifetime risk of ovarian cancer, those with a breast cancer 2 (BRCA2) gene mutation have a 13 to 23% risk, those with Lynch syndrome (hereditary nonpolyposis colorectal cancer) have a 3 to 14% risk, and the general population has a 1.5% lifetime risk. In women with BRCA mutations, BSO is performed after childbearing is completed and this is associated with an 80% reduction in ovarian cancer and a 30 to 75% reduction in breast cancer. Still, these women continue to have a 2% risk of developing peritoneal serous carcinoma and require an annual pelvic examination with estimation of serum CA 125 level. Women who are at average risk (general population risk) or who have isolated risk factors are not candidates for risk-reducing BSO and need alternate methods to reduce their risk of developing ovarian cancer. One of these methods was a common gynecologic practice of performing an elective BSO at the time of hysterectomy for a benign condition in women beyond 45 years of age. An elective BSO is the removal of ovaries and fallopian tubes in a woman with no known indication for this procedure (e.g. ovarian pathology, hereditary ovarian cancer syndrome). When performed before the age of natural menopause (median age 51 years), elective BSO leads to a surgical menopause which is characterized by an abrupt drop in estrogen levels and the complete cessation of ovarian hormone production (androgens, estradiol, progesterone). By contrast, transition into natural menopause has a gradual waning of estradiol levels over about 4 years, which continues up to 10 years. Postmenopausal ovaries are hormonally active for many years, producing small amounts of androgens, estradiol and estrone.

The long-term health outcomes after an elective BSO compared with ovarian conservation at time of hysterectomy need to be addressed: essentially it is a trade-off between reduction (though not elimination) in the risk of ovarian cancer *vs* the unfavorable consequences of an abrupt (surgical) menopause. Data from the nurses' health study showed that elective BSO reduced the risk of ovarian cancer mortality [hazard ratio (HR) 0.06, 95% confidence interval (CI) 0.02-0.17]. In addition, there was a significant reduction in breast cancer incidence but only in women who underwent this at 47.5 years age or less. On the contrary, elective BSO at a younger age was associated with increased all-cause mortality (HR 1.13, 95% CI 1.06-1.21), especially among women who did not take estrogen replacement therapy. The potential reason for the increased all-cause mortality is hypoestrogenism. It was associated with an increase in death due to lung cancer (HR 1.29, 95% CI 1.04-1.61) and colorectal cancer (HR 1.49, 95% CI 1.02-2.18). Elective BSO at a younger age and in premenopausal women was associated with an increased risk of cardiovascular disease [relative risk (RR) 2.62, 95% CI, 2.05-3.35] and an increased risk of cognitive impairment or dementia, parkinsonism, depression and anxiety. Estrogen replacement may offset these risks to some extent and is recommended until the median age of natural menopause. Data about increased risk of glaucoma following elective BSO are also emerging. Sexual dysfunction is more common after surgical menopause *vs* natural menopause, probably because surgical menopause is associated with an abrupt decrease in androgen level. Osteoporotic fractures may also be increased. All these

effects are a result of removal of the healthy functioning ovaries and not due to removal of the fallopian tubes. Hence, the decision of whether to conserve the ovaries or not at the time of hysterectomy in premenopausal women is complex and should take both the benefits and risks into account. The American College of Obstetrics and Gynecology (ACOG) advises strong consideration of ovarian conservation at time of hysterectomy in premenopausal women who are not at an increased genetic risk of ovarian cancer. They advise consideration of oophorectomy at time of hysterectomy in women who are postmenopausal or who have a condition that may benefit from oophorectomy (e.g. endometriosis, pelvic inflammatory disease, chronic pelvic pain). Women who undergo oophorectomy inducing premature (before age 40 years) or early (before age 45 years) menopause are likely to benefit from estrogen therapy until they reach the age of natural menopause.

Recent data suggest that some ovarian cancers are actually initiated in the fallopian tubes, thus removal of the fallopian tubes (bilateral salpingectomy) may be a risk-reducing strategy in both high-risk and average-risk women. Traditionally, most malignant epithelial ovarian lesions were considered to be primary ovarian disease, and primary tubal or peritoneal cancers were thought to be rare. However, current data suggest that some apparent ovarian serous carcinomas begin in the fallopian tubes and then spread to the ovary. Evaluation of the fallopian tube specimens from risk-reducing BSO procedures in women with BRCA1 and BRCA2 mutations has revealed occult carcinomas and preinvasive lesions in 5 to 15% of the fallopian tubes but not in the ovaries. Preinvasive lesions in the distal fallopian tubes [serous tubal intraepithelial neoplasia (STIN)] have been identified in 1 to 6% of high-risk women undergoing risk reducing BSO. Serous tubal intraepithelial carcinoma (STIC), and invasive serous carcinomas are also identified in the distal fimbrial end of the fallopian tubes in women with nonfamilial or sporadic 'ovarian' cancer; in the PGI experience (unpublished data, Dr Radhika Srinivasan et al), it was observed in about 60% cases similar to the experience from other centers. These lesions originating in the tubal fimbria may spread to the peritoneum and result in apparent primary peritoneal carcinoma without an ovarian lesion. Thus, serous ovarian, fallopian tubal and peritoneal carcinomas are regarded as a single entity and designated as 'pelvic serous carcinoma'. Based upon these findings, it is proposed that tubal neoplasia is the primary lesion in high-grade serous pelvic carcinomas and that these lesions subsequently spread to the ovary and peritoneum. Therefore, it is possible that the risk of developing high-grade serous pelvic carcinomas may be reduced by salpingectomy. An 'opportunistic' salpingectomy is the removal of the fallopian tubes for primary prevention of epithelial carcinoma of the fallopian tube, ovary or peritoneum in a woman undergoing pelvic surgery for another indication. This is an approach for prevention in women at average risk (but not at high risk who should undergo a BSO) from these cancers. It is appropriate in women who have completed childbearing. If there are no indications for oophorectomy, the ovaries are conserved. Traditionally, the surgical removal or preservation of the fallopian tubes depended upon the surgical plan for the ovary. But, this is changing now and the fallopian tubes are viewed as independent entities responsible for many (if not most) of the cases of epithelial ovarian cancer.

Procedures that may include an opportunistic salpingectomy are a hysterectomy for benign indications and in place of tubal ligation for women who desire sterilization. The society of gynecology oncology suggests that for premenopausal women at average risk of ovarian cancer, risk-reducing salpingectomy (without oophorectomy) should be discussed and considered with patients at the time of abdominal or pelvic surgery, hysterectomy or in lieu of tubal ligation. In January 2015, the ACOG expressed an opinion stating that 'salpingectomy at the time of hysterectomy or as a means of tubal sterilization appears to be safe, without an increase in complications. Salpingectomy while leaving the ovaries intact may be better for cancer prevention than BSO. More randomized trials are needed to support the use of salpingectomy in reducing ovarian cancer'. A word of caution about complete salpingectomy for tubal sterilization: it cannot be reversed, unlike the currently used tubal sterilization techniques. The demand for reversal of tubal sterilization is highest in women <30 years of age or who undergo this within 3 years of the youngest child. Women considering opportunistic salpingectomy in lieu of tubal sterilization should be clearly informed that there is no possibility of a reversal of tubal sterilization.

Opportunistic salpingectomy is not a replacement for risk-reducing BSO in women at high risk. It is a risk-reducing strategy for women at average or population risk. The goal of opportunistic salpingectomy is removal of the distal one-third (fimbria and infundibulum, portion of ampulla) of both fallopian tubes. Research has shown that the distal fimbriated end harbors the majority of cancers and preinvasive lesions in both the general population and BRCA1 and BRCA2 mutation carriers. Opportunistic salpingectomy was introduced in 2010, and there are no data regarding long-term impact on ovarian, tubal and peritoneal carcinoma rates or ovarian function. It will take at least 10 years of data regarding the procedure to see if there is a decrease in the rate of ovarian cancers.

To conclude the practice of counseling women planning a hysterectomy for benign indications and were in their mid-40s or older, to undergo concomitant BSO is now replaced by consideration of elective salpingectomy alone, and conserving the normal ovaries. This is the current primary prevention strategy being adopted in women at general population risk of ovarian cancer.

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