Case 3: Risk-reducing salpingo-oophorectomy

Susan is now 40 years of age with a feisty 4 year-old and has decided to undergo a risk-reducing salpingo-oophorectomy (RRSO) because she carries a *BRCA1* mutation. Susan's gynecologist performs a laparoscopic RRSO. After surgery, Susan meets with her doctor to review the pathology report, which shows some atypical cells in the fallopian tubes, called serous tubal intraepithelial carcinoma (STIC).

Questions

Are any special procedures part of a RRSO?

RRSO is usually performed as a minimally invasive (laparoscopic) surgery that takes approximately 60 to 90 minutes. This outpatient surgery usually requires several small incisions. The abdomen is inspected thoroughly and a pelvic wash is collected for cytology to see if abnormal cells are present before the fallopian tubes and ovaries are manipulated. The blood supply to the ovary and tube is interrupted at 2 cm or more away from the ovary to ensure that all the ovarian tissue is removed. As much fallopian tube as possible is carefully removed from its junction with the uterus. An initial inspection by the pathologist is performed during the procedure to see if obvious cancer is present. After surgery, the ovaries and tubes are cut into 2-3 mm sections so that each section can be carefully examined by the pathologist for early cancer or pre-cancer. This special pathology procedure is critical to detect microscopic cancer and differs from the typical processing of tubes and ovaries for benign gynecologic surgery. The entire fallopian tube must be examined in careful detail as most of the pre-cancer and early cancer changes are found in the fallopian tube rather than the ovary.

What is the benefit of RRSO?

RRSO prevents approximately 80% of ovarian/fallopian tube and peritoneal cancer in women who carry *BRCA1* and *BRCA2* mutations. Current guidelines recommend RRSO for women between the ages of 35 and 40, although delaying until mid-forties in women with *BRCA2* mutations may be considered because the incidence of ovarian cancer is approximately 1% for women under age 50. Breast cancer risk may also be reduced by premenopausal RRSO. One study has shown that RRSO surgery also reduces death from all causes in women with *BRCA1* and *BRCA2* mutations as well as deaths specifically from breast and ovarian cancer. One caution is that women can still get primary peritoneal carcinoma, an ovarian-like cancer, after RRSO; however, the risk is very low, particularly when the ovaries and fallopian tubes are removed in their entirety and carefully examined for early cancers.

Should hysterectomy be performed along with RRSO?

Generally, the uterus and cervix are not at high risk for cancer in the same way the fallopian tubes and ovaries are in patients with *BRCA1* and *BRCA2* mutations, although data have suggested a small increased risk of serous endometrial cancer in *BRCA1* mutation carriers. Since serous uterine cancer is difficult to detect early, some women choose to have a hysterectomy at the time of RRSO in order to have maximum gynecologic cancer risk reduction. Another potential advantage of hysterectomy performed at the time of risk-reducing surgery is to facilitate postoperative hormonal therapy; if hysterectomy were performed, only estrogen would be needed, which confers lower risk of hormone therapy complications compared to combined therapy with estrogen and progestin. Some women choose hysterectomy because they are on tamoxifen for breast cancer risk reduction, which is associated with an increased uterine cancer risk. Still others may have gynecologic reasons for desiring hysterectomy, such as fibroids or abnormal Pap smears. An argument against hysterectomy is a small increase in recovery time and surgical complications associated with the addition of hysterectomy to salpingo-oophorectomy. Generally, the decision to include hysterectomy with RRSO in *BRCA1* and *BRCA2* mutation carriers should be based on a full discussion of risks and potential benefits in shared decision-making between the patient and her surgeon.

What is the significance of serous tubal intraepithelial carcinoma (STIC)?

STIC was first identified in the fallopian tube specimens removed from women with a *BRCA1* or *BRCA2* mutation. It comprises cancer cells that are confined to the innermost layer of the fallopian tube, called the mucosal epithelium, that have not yet invaded to deeper tissues as a true invasive carcinoma would. They are almost always found on the fimbriae, the ends of the fallopian tubes furthest from the uterus.

STIC or invasive cancers are identified in 4-10% of women with *BRCA1* and *BRCA2* mutations when complete serial sectioning of the fallopian tubes is performed at RRSO. Pre-invasive and invasive lesions are more commonly

found in women with *BRCA1* mutations over age 45 at the time of surgery.

The management of women in whom only STIC but no invasive cancer is identified is not well established. The risk that a STIC will develop into an invasive carcinoma in the tube or spread to the ovary is not known. Pelvic washings are sometimes positive for abnormal cells in women in whom STIC has been identified, raising the possibility that a small cancer may have already spread to the peritoneal surfaces.

Based on an uncertain risk of developing carcinoma in the future, management protocols for women with STIC have ranged from surveillance to surgical staging and consideration of chemotherapy. CA-125 levels are usually normal but may be helpful to raise suspicion of more extensive disease. Each patient with STIC should discuss her options with her gynecologic oncologist.

What is the association of fallopian tube cancer with *BRCA1* and *BRCA2* mutations?

When STIC and invasive fallopian tube cancer were seen in RRSO specimens from women with *BRCA1* and *BRCA2* mutations, experts realized that the fallopian tube, rather than the ovary, might be the originating site of many pelvic serous cancer cases. This has changed the thinking about the prevention of "ovarian" cancer to include an emphasis on the fallopian tube. The increased risk of ovarian cancer associated with *BRCA1* and *BRCA2* mutations is more accurately stated as an increased risk of pelvic serous cancers, including fallopian tube, ovarian and peritoneal cancers.

Are there surgical alternatives to RRSO?

Tubal ligation and hysterectomy have been associated with some risk reduction for ovarian cancer. More recently, risk-reducing salpingectomy has been suggested as a bridge to delayed oophorectomy in young women with *BRCA1* and *BRCA2* mutations who desire risk reduction that avoids menopause. Delaying oophorectomy, however, negates the risk reduction for breast cancer in these women. In addition, cases of pelvic cancer arising in the ovaries would not be prevented. Salpingectomy instead of BSO has not yet been fully evaluated as to safety or effectiveness in women at high risk of ovarian cancer. Observational trials are ongoing in the United States and Europe to collect more information about this alternative.

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