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Committee on Gynecologic Practice

The Role of the Obstetrician–Gynecologist in the Early Detection of Epithelial Ovarian Cancer

ABSTRACT: Epithelial ovarian cancer is most commonly detected in an advanced stage, when the overall 5-year survival rate is 20–30%. Detection of early-stage ovarian cancer results in improved survival. Currently, there is no effective strategy for ovarian cancer screening. Women with persistent and progressive symptoms, such as an increase in bloating, pelvic or abdominal pain, or difficulty eating or feeling full quickly, should be evaluated, with ovarian cancer being included in the differential diagnosis. Evaluation of the symptomatic patient includes physical examination and may include transvaginal ultrasonography and measurement of levels of the serum tumor marker CA 125. Patients suspected of having ovarian cancer should be managed by a gynecologic surgeon, such as a gynecologic oncologist, who is trained to perform comprehensive surgical staging and cytoreductive (debulking) surgery.

Although ovarian cancer is the second most common type of female reproductive cancer, more women die from ovarian cancer than from cervical cancer and uterine cancer combined. It is estimated that in the United States in 2010, ovarian cancer was diagnosed in 21,880 women and 13,850 women died from this malignancy. The principal reason for these poor outcomes is the advanced stage of epithelial ovarian cancer at diagnosis (70–75% of cases are stage III or stage IV and have an overall 5-year survival rate of only 20–30%). However, women with stage I disease have a 90–95% probability of cure. The purpose of this Committee Opinion is to define the role of the generalist obstetrician–gynecologist in the early detection of epithelial ovarian cancer.

Screening of Low-Risk Women

The use of transvaginal ultrasonography and tumor markers (such as CA 125) as potential screening strategies have been evaluated. These methods, however, have proved ineffective for screening low-risk asymptomatic women because their sensitivity, specificity, positive predictive value (PPV), and negative predictive value all have been modest at best (1). Because of the low prevalence of epithelial ovarian cancer, reported to be approximately 1 case per 2,500 women per year, it has been estimated that a test with even 100% sensitivity and 99% specificity would have a PPV of only 4.8%, which means 20 of 21 women undergoing surgery would not have primary ovarian cancer (2).

Transvaginal Ultrasonography

Transvaginal ultrasonography may detect changes in ovarian size and morphology before signs or symptoms of cancer develop. The upper limit of normal ovarian volume has been defined as 20 cm^3 in premenopausal women who are not pregnant and 10 cm^3 in postmenopausal women (3). Adding cyst wall characteristics and the presence of septae to the measurement of ovarian volume resulted in a sensitivity of 86% and a specificity of 99% for differentiating benign lesions from malignant lesions (4). A finding of increased blood flow in the ovary by Doppler ultrasonography also has been suggested as a means of identifying malignant lesions.

Some ovarian cancer screening trials involving the use of transvaginal ultrasonography have demonstrated a trend toward an early-stage ovarian cancer diagnosis (5–12). The PPV of ultrasonography in these studies of more than 136,000 women varied from 1.0% (10) to 27% (8); however, the latter study included mostly women at high risk because of a family history of breast cancer or ovarian cancer, and because of its nonrandomized and uncontrolled design, is insufficient to support claims that screening results in an improved survival rate.

CA 125 Serum Tumor Marker

The potential advantages of measuring serum tumor markers for ovarian cancer detection include availability and repeatability, minimal invasiveness, operator independence, and lower cost than ultrasonography. The tumor marker CA 125, a monoclonal antibody that detects ovarian cancer antigen OC 125, is the most extensively evaluated serum marker for cancer screening and has been evaluated alone and in combination with other markers.

Initial studies showed that the CA 125 levels were elevated in approximately 80% of women with epithelial ovarian cancer (13). However, subsequent studies have demonstrated both poor sensitivity and specificity for early-stage cancer detection (14, 15). Measuring the CA 125 level may predict cancer more accurately in postmenopausal women than in premenopausal women, with specificity values reported as 98.5% for women older than 50 years and an unacceptable 94.5% for those younger than 50 years (16). Measuring CA 125 levels over time provides a more accurate assessment of ovarian cancer risk than does a one-time measurement (17). In a prospective study of postmenopausal women, such a serial measure, called the Risk of Ovarian Cancer algorithm, was found to have a PPV of 19% (18).

Combining CA 125 with other markers in tumor marker panels has been shown to increase sensitivity by 5–10%; however, specificity is decreased (19). Initial analysis of a tumor marker panel that included CA 125, leptin, prolactin, osteopontin, insulin-like growth factor II, and macrophage inhibitory factor was reported to significantly improve sensitivity and specificity (20). However, because of serious methodologic limitations of the study, the results were greatly overestimated (21, 22), and PPV was only 6.5% when recalculated at the true prevalence of the disease (20). Tumor marker panels have not been evaluated prospectively in large population-based studies and have not been proved to improve early detection and survival rates.

Studies on Combined Modality Screening

Ultrasonography and measurement of tumor markers alone have not demonstrated the sensitivity, specificity, and PPV necessary to justify their use for ovarian cancer screening in average-risk populations of postmenopausal women. Large-scale prospective randomized trials in both the United States and the United Kingdom have been initiated to address the virtue of combined modality assessment for screening.

The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial is a U.S.-based randomized controlled trial that has enrolled 34,261 healthy average-risk women between the ages of 55 years and 74 years to receive either annual CA 125 testing plus transvaginal ultrasonography or "usual care," which includes annual pelvic examination (10). Based on interim results from the screening period, the PPV of this combination testing in the average-risk population was 1.3%. Long-term follow-up is not yet complete, and final results are anticipated in 2014.

The United Kingdom Collaborative Trial of Ovarian Cancer Screening has enrolled more than 202,000 postmenopausal women between the ages of 50 years and 74 years. Women of average risk have been randomized to receive either annual pelvic examination, annual ultrasonography, or CA 125 measurement (including the Risk of Ovarian Cancer algorithm), with ultrasonography for elevated CA 125 levels (23). Preliminary results suggest a more favorable proportion of early-stage ovarian cancer detection (48%) with either transvaginal ultrasonography or CA 125 measurement (plus ultrasonography, as indicated). Specificity of CA 125 measurement (plus indicated ultrasonography) was 99.8% and that of ultrasonography alone was 98.2%. The PPV of CA 125 measurement and ultrasonography, as indicated, was 35.1%. However, despite these promising results, it is important to await the longer-term follow-up data with respect to survival.

Screening of High-Risk Women

Factors known to increase the risk of ovarian cancer include an identified *BRCA* gene mutation and a family history of cancer, which is suggestive of a hereditary cancer syndrome. Women with these conditions should be referred for formal genetic counseling to better assess their cancer risk, including risk of ovarian cancer. If appropriate, these women may be offered ovarian cancer screening. Screening with CA 125 measurement and transvaginal ultrasonography every 6 months has been recommended for high-risk women by the National Comprehensive Cancer Network (24), although evidence is insufficient to demonstrate that current screening methods improve survival rates for these women (25–29). The American College of Obstetricians and Gynecologists recommends that risk-reducing salpingo-oophorectomy, which includes removal of the ovaries and fallopian tubes in their entirety, be offered by age 40 years for women with *BRCA1* or *BRCA2* mutations (30).

Evaluation of Women With Signs or Symptoms

Past descriptions of ovarian cancer as the "silent" cancer are a misconception. Recent studies have shown that women with ovarian cancer may develop symptoms several months before the diagnosis, even with early-stage disease. In a survey of 1,725 women with ovarian cancer, 70% recalled having symptoms for 3 months or longer before the diagnosis, and 35% recalled having symptoms for at least 6 months (31). Approximately three fourths of these women had abdominal symptoms and one half had pain or constitutional symptoms. This initial research led to further studies to define which symptoms are most associated with ovarian cancer. In a case–control study of women between the ages of 15 years and 90 years, researchers compared the frequency of symp-

toms typical in ovarian cancer reported by 1,709 women being evaluated in a primary care clinic with those reported by 128 women undergoing surgery for a pelvic mass (32). Symptoms such as increased abdominal size, bloating, urinary urgency, and pelvic pain were found more frequently in women with ovarian cancer. Women with cancer reported that their symptoms occurred 20–30 times per month as compared with two to three times per month for the women seen in the primary care clinics. The study pointed out that although these symptoms experienced by women with ovarian cancer and those presenting to primary care clinics are similar, the frequency, severity, and duration of these symptoms were greater in women with ovarian cancer. Although this information is compelling, it is not from a prospective trial, and patient recall bias may have influenced the results. However, based on this information, an ovarian cancer symptom index was developed (33). Factors that were most significantly associated with ovarian cancer, if they occurred more than 12 days per month and for less than 1 year, were pelvic or abdominal pain, increase in abdominal size or bloating, and difficulty eating or feeling full. When tested in a confirmatory sample, this ovarian cancer index had a sensitivity of 56.7% for women with early-stage disease and 79.5% for those with late-stage disease, with a specificity of 86.7% for women younger than 50 years and 90% for women older than 50 years.

Two other studies have disputed the value of the symptom index to detect early ovarian cancer. In a study that tested the symptom index in a group of patients undergoing transvaginal ultrasonography as part of a screening trial, only 20% of women with ovarian cancer acknowledged that they had symptoms (34). In another study, in-person interviews were conducted with 812 patients with ovarian cancer and 1,313 control participants. Symptoms were less likely to be present in women with early-stage ovarian cancer. The estimated PPV of the symptom index was 0.6% for late-stage disease and less than 0.5% for early-stage disease (35).

Currently, it appears that the best way to detect ovarian cancer is for both the patient and her clinician to have a high index of suspicion of the diagnosis in symptomatic women. This requires education of both as to the symptoms commonly associated with ovarian cancer. Persistent and progressive symptoms such as an increase in bloating, pelvic or abdominal pain, or difficulty eating or feeling full quickly, should be evaluated, with ovarian cancer being included in the differential diagnosis.

In evaluating these symptoms, physicians should perform a physical examination, including a pelvic examination. A rectovaginal examination may provide additional information. Imaging studies, especially transvaginal ultrasonography, may be helpful in recognizing increased ovarian size or morphologic changes associated with ovarian cancer.

In premenopausal women with symptoms, a slightly elevated CA 125 value may be misleading because elevated levels of CA 125 are associated with a variety of common benign conditions, including uterine leiomyomas, pelvic inflammatory disease, endometriosis, adenomyosis, pregnancy, and even menstruation. Nonetheless, extremely high levels of CA 125 may be useful in the evaluation of premenopausal women. In postmenopausal women with a pelvic mass, a CA 125 measurement may be helpful in predicting a higher likelihood of malignancy. This information may be useful in making consultation or referral decisions. However, a normal CA 125 measurement alone does not rule out ovarian cancer because more than 50% of cases of early-stage cancer and 20–25% of cases of advanced cancer are associated with normal values.

The U.S. Food and Drug Administration has recently cleared for marketing a qualitative serum test, which appears to improve the predictability of ovarian cancer in women with pelvic masses (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2009/ucm182057.htm). This is not a screening test, but it may be useful for evaluating women with a pelvic mass. The test evaluates five biomarkers: 1) transthyretin, 2) apolipoprotein A-1, 3) β2 microglobulin, 4) transferrin, and 5) CA 125 II (36). This test is cleared for use in women older than 18 years, with an already detected ovarian adnexal mass needing surgery. Clinical utility is not yet established.

When physical examination and imaging techniques have detected the presence of a pelvic mass that is suspicious for a malignant ovarian neoplasm, the presence of at least one of the following indicators warrants consideration of referral to or consultation with a physician trained to appropriately stage and debulk ovarian cancer, such as a gynecologic oncologist:

- Postmenopausal women: elevated CA 125 level, ascites, a nodular or fixed pelvic mass, or evidence of abdominal or distant metastasis
- Premenopausal women: very elevated CA 125 level, ascites, or evidence of abdominal or distant metastasis

When a patient with a suspicious or persistent complex adnexal mass requires surgical evaluation, a physician trained to appropriately stage and debulk ovarian cancer, such as a gynecologic oncologist, should perform the operation. This should be done in a hospital facility that has the necessary support and consultative services (eg, frozen section pathology) to optimize the patient's outcome. When a malignant ovarian tumor is discovered and the appropriate operation cannot be properly performed, a gynecologic oncologist should be consulted intraoperatively if possible.

Surgical Staging

Patients whose comprehensive surgical staging confirms early-stage disease have a much better prognosis than those patients who are thought to have early-stage dis-

ease but do not undergo comprehensive surgical staging, presumably because occult metastatic disease was missed. In the absence of clinically apparent malignant disease, an intraoperative pathology consultation should be obtained if cancer remains a concern. If an apparent early-stage malignancy is present, comprehensive surgical staging should be performed, preferably during the same operation. The surgical procedure should include obtaining peritoneal cytology when the abdomen is entered. The adnexal mass should be removed intact through an incision that permits thorough staging and surgical management of the primary tumor and possible sites of metastasis. The liver, spleen, and all peritoneal surfaces, including both hemidiaphragms, should be inspected and palpated. Further staging should include an omentectomy, bilateral pelvic and paraaortic lymphadenectomy, peritoneal biopsies, removal of the uterus and adnexa, and removal of any suspicious lesions.

When the cancer appears to be confined to one ovary, especially if it is low grade, it is appropriate to modify the staging procedure by leaving the uterus and the uninvolved ovary in place for younger women who wish to preserve their fertility.

Conclusions

- Epithelial ovarian cancer is most commonly detected in an advanced stage, when the overall 5-year survival rate is 20–30%.
- Detection of early stage ovarian cancer results in improved survival.
- There is currently no effective strategy for ovarian cancer screening.
- The obstetrician–gynecologist should be aware that there may be symptoms (including increased abdominal size or bloating, abdominal or pelvic pain, or feeling full quickly or difficulty eating) associated with ovarian cancer that should be investigated.
- Evaluation of the symptomatic patient includes physical examination and may include transvaginal ultrasonography and measurement of levels of the serum tumor marker CA 125.
- When a patient with a suspicious or persistent complex adnexal mass requires surgical evaluation, a physician trained to appropriately stage and debulk ovarian cancer, such as a gynecologic oncologist, should perform the operation.

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