"Know Your Body.
Know The Symptoms.
Help Spread The Word."

Symptom and Guidance Tools

This packet contains **two tools** that women can use to pursue answers to their concerns that the symptoms they are experiencing may be evidence of ovarian cancer.

The first tool is a personal **Symptom Diary**, adapted by the Ovarian Cancer National Alliance and the Gynecologic Cancer Foundation, which can be used to track persistency of symptoms over time that may indicate the possibility of ovarian cancer. Completing this diary will help you document your concerns and assist you and your doctor in determining next steps.

The second tool is an **Interim Practice Guidance*** and outlines important steps your doctor may take to evaluate whether your symptoms may be ovarian cancer. Leaders in ovarian cancer research, diagnosis and treatment have developed these symptom management strategies based on their expertise and years of practice. The Ovarian Cancer National Alliance believes this very important information should be shared publicly to help women with ovarian cancer get diagnosed sooner.

In order to help physicians consider ovarian cancer as a potential diagnosis when evaluating women who present with certain symptoms, the following guidance is based on expert opinion, and will be revised as clinical data becomes available. The Ovarian Cancer National Alliance will continue to work with the medical community to ensure that women are diagnosed with ovarian cancer earlier, when intervention can make the greatest difference in survival and women can live longer, healthier lives.

Because the symptoms of ovarian cancer often mimic other conditions, they are sometimes misdiagnosed or ignored. By tracking the persistency of the symptoms, over time women will be better able to discuss their options for further diagnostics with their doctors. By using the **Symptom Diary** and the **Interim Guidance**, we believe that more women will be diagnosed with ovarian cancer earlier and hope that lives can be saved.

**The views and opinions presented in the guidance are solely those of the individual authors and do not necessarily represent those of the organizations with which they are affiliated.*

Ovarian Cancer National Alliance
We work to save women's lives

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Introduction to Diary

This Symptom Diary is designed to help you communicate clearly with your doctor, (preferably a gynecologist) about symptoms that are persistent (for more than a month) and may be indicative of ovarian cancer. We encourage you to use the Diary as a tool to more accurately describe your symptoms to your doctor. The Diary should reveal persistency and severity.

Using this Diary will help your doctor understand your symptoms, and whether ovarian cancer should be a consideration in your diagnosis. Early detection may lead to a better chance of a positive outcome.

Remember that ovarian cancer is not common but neither is it rare. Women are advised to remember that the presence of symptoms *may not indicate* ovarian cancer, but that *persistency of symptoms* requires closer investigation. However, early diagnosis improves your chances for a positive outcome, so it is important that you tell your doctor if symptoms are persistent and different from what is normal for you.

Next Steps:

Make an appointment with your doctor and take the Diary with you to the visit. The Diary will provide your doctor a clear image of what you are experiencing.

Your doctor should consider the possibility of ovarian cancer if symptoms are frequent, persistent, new to you and otherwise unexplained. Your doctor can arrange the following tests:

- CA-125 blood test
- Transvaginal ultrasound
- Manual pelvic and rectal exam

If any of these results suggest that ovarian cancer is a possibility, it is important that you be referred to a gynecologic oncologist as soon as possible.

Diary initially developed in the United Kingdom by Ovarian Cancer Action.

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GCF Gynecologic Cancer Foundation

"Know Your Body.
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Symptoms Diary: Persistence Matters!

If you experience any of these **symptoms**, circle the days you experience the symptom. For example, if you have abdominal pain on Tuesday and Wednesday during the same week, circle those days.

If you have any of these symptoms almost daily for more than a month, **please see your doctor** (preferably a gynecologist) right away.

	Bloating	Pelvic/ Abdominal Pain	Difficulty eating or feeling full quickly	Urinary Symptoms	Other Symptoms
Week 1	Sunday Monday Tuesday Wednesday Thursday Friday Saturday	Sunday Monday Tuesday Wednesday Thursday Friday Saturday	Sunday Monday Tuesday Wednesday Thursday Friday Saturday	Sunday Monday Tuesday Wednesday Thursday Friday Saturday	
Week 2	Sunday Monday Tuesday Wednesday Thursday Friday Saturday	Sunday Monday Tuesday Wednesday Thursday Friday Saturday	Sunday Monday Tuesday Wednesday Thursday Friday Saturday	Sunday Monday Tuesday Wednesday Thursday Friday Saturday	
Week 3	Sunday Monday Tuesday Wednesday Thursday Friday Saturday	Sunday Monday Tuesday Wednesday Thursday Friday Saturday	Sunday Monday Tuesday Wednesday Thursday Friday Saturday	Sunday Monday Tuesday Wednesday Thursday Friday Saturday	
Week 4	Sunday Monday Tuesday Wednesday Thursday Friday Saturday	Sunday Monday Tuesday Wednesday Thursday Friday Saturday	Sunday Monday Tuesday Wednesday Thursday Friday Saturday	Sunday Monday Tuesday Wednesday Thursday Friday Saturday	

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Introduction to Guidance

Annually, more than 15,000 women die from ovarian cancer. Survival rates have remained steady near 40% for years, primarily due to the lack of a reliable early detection test. Recently, studies have shown that women with ovarian cancer do present with symptoms that could alert them and their physicians to suspect ovarian cancer as a potential cause.

If the following symptoms are frequent and persist for more than a month, are unusual for a woman and are otherwise unexplained, the Ovarian Cancer National Alliance advises that she have an evaluation for ovarian cancer. These symptoms include:

- Bloating
- Pelvic or abdominal pain
- Difficulty eating or feeling full quickly
- Urinary symptoms (urgency or frequency)

Those women with a family history of cancer or other risk factors (such as a strong family history of breast and ovarian cancer or of a high-risk genetic syndrome) should follow existing protocols for management of ovarian cancer in high risk women.

The attached guidance is for women of average risk. A summary of this information follows.

1. Women who have symptoms of ovarian cancer repeatedly (more than 12 times per month) and the symptoms are new, should receive a manual pelvic and rectal exam.

2a. If that exam shows abnormalities that may indicate ovarian cancer, a transvaginal ultrasound (TVS) and CA-125 blood test should be performed. Note: the TVS should be performed by a sonographer experienced in using TVS to detect ovarian cancer.

2b. If the manual exam is normal but symptoms persist, a TVS and CA-125 blood test should be performed.

3a. If the results of both tests are normal, consider other causes and repeat the test in 3 months if symptoms persist.

3b. If the CA-125 is abnormal but the TVS is normal, do another blood test in 6 weeks.

3c. If the CA-125 is normal but the TVS is abnormal, refer to an expert such as a gynecologic oncologist.

3d. If both tests are abnormal, refer to an expert such as a gynecologic oncologist.

Our goal in providing this guidance is to help diagnose ovarian cancer in its earliest stage, when the probability of a good result from treatment is higher.

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Interim Guidance for the Management of Average-Risk Women with Symptoms Suggestive of Ovarian Cancer

Abstract

Ovarian cancer is the leading cause of death from gynecologic cancers in the United States. Survival is better when ovarian cancer is diagnosed early, but most cancers are diagnosed at an advanced stage when survival is poor. Attempts to develop early detection tests and screening strategies have produced promising preliminary results but have not provided sufficient evidence to support routine screening recommendations. Other studies have investigated the occurrence of symptoms in patients prior to diagnosis, and suggested that symptom recognition as part of a multimodal strategy may lead to earlier diagnosis and more successful treatment. Patients with frequent, unexplained symptoms of recent onset should be evaluated for ovarian cancer. Management strategies using the serum marker CA-125 and transvaginal ultrasound are proposed. The effect of symptom-based intervention on survival of women found to have ovarian cancer is at this time unknown.

Introduction

Ovarian cancer accounts for more deaths than any other cancer of the female reproductive tract. The American Cancer Society estimates there will be 21,650 new cases of the disease and 15,520 deaths in 2008.[1] Unfortunately 65-70% of ovarian cancers are diagnosed at an advanced stage, when prognosis is poor.

Many women diagnosed with ovarian cancer recall having symptoms prior to diagnosis; other patients may have minimal or no symptoms. Several retrospective and prospective case-control studies have revealed that over 90 percent of ovarian cancer patients reported symptoms prior to diagnosis, including 80-90 percent of patients with early stage disease.[2-6] One study surveyed women seeking care at primary care clinics and a smaller group of women in whom an ovarian mass had been detected; the latter group was surveyed prior to surgery and diagnosis, thus decreasing the potential role of recall bias.[6] Another study reviewed Medicare claims records for symptoms-related diagnoses among ovarian cancer patients and controls in California. Symptoms were more common in patients with ovarian cancer, prior to diagnosis, than in the control group.[7] While it is uncertain that early identification of ovarian cancer based on symptoms will lead to earlier stage diagnosis or improved survival, there may be benefit to a careful evaluation of patients who present with frequent symptoms that are new and otherwise unexplained.

Because symptoms of ovarian cancer are common to other chronic conditions and may be transitory, identifying which patients should be referred for diagnostic evaluation is a complex challenge for the average clinician.[6, 8-9] The low prevalence of this disease and the difficulty of confirming diagnosis without intraperitoneal sampling necessitate screening and diagnostic tests with high positive predictive value and specificity. Currently, there are no screening tests that have yet been shown to have sufficient accuracy and benefit to be used for screening in the general population. However, because of the suggestion that certain symptoms might identify ovarian cancer patients even in early stages, guidance about management of average-risk women with symptoms suggestive of ovarian cancer is appropriate. For such patients, the most useful clinical approach, based on expert opinion and limited data, is described herein. While it is not known yet whether the proposed management strategies will impact prognosis, most cancers are most successfully treated when tumor volume is small and stage is early.

Symptom Evaluation

Non-specific symptoms suggestive of ovarian cancer have been described in a national consensus statement (June 2007) issued by the Gynecologic Cancer Foundation, the Society of Gynecologic Oncologists, and the American Cancer Society.[8] The symptoms most commonly associated with

ovarian cancer include bloating, pelvic or abdominal pain, difficulty eating or feeling full quickly, and urinary urgency or frequency.[9] These symptoms are more likely to persist in women with ovarian cancer than women in the general population, but are not unique to ovarian cancer and, when cancer is present, are not unique to early stage disease. Based on studies to date, there are no unique symptoms that distinguish early from late stage ovarian cancer.

Women with ovarian cancer have reported that they experience symptoms that are persistent and represent a change from their normal baseline. Frequency and duration (<12 months) of symptoms were found to be associated with the diagnosis of ovarian cancer.[6, 9] Women with ovarian cancer were more likely to experience symptoms >12 times per month and often 20-30 times per month compared to 2-3 times per month for controls.[9] If symptoms are new and occur repeatedly for at least a month and are otherwise unexplained, an evaluation for ovarian cancer is recommended.

The primary challenge facing the clinician in dealing with symptoms of ovarian cancer is that the most common symptoms are also symptoms commonly associated with syndromes of gastrointestinal dysfunction. Published reports have shown that assessing the frequency and duration of symptoms greatly improves their predictive value for the presence of ovarian cancer. Goff and colleagues, for example, found that women with malignant ovarian masses reported having symptoms for 6 months or less compared to women with irritable bowel syndrome (IBS) who reported having symptoms for 12-24 months.[6]

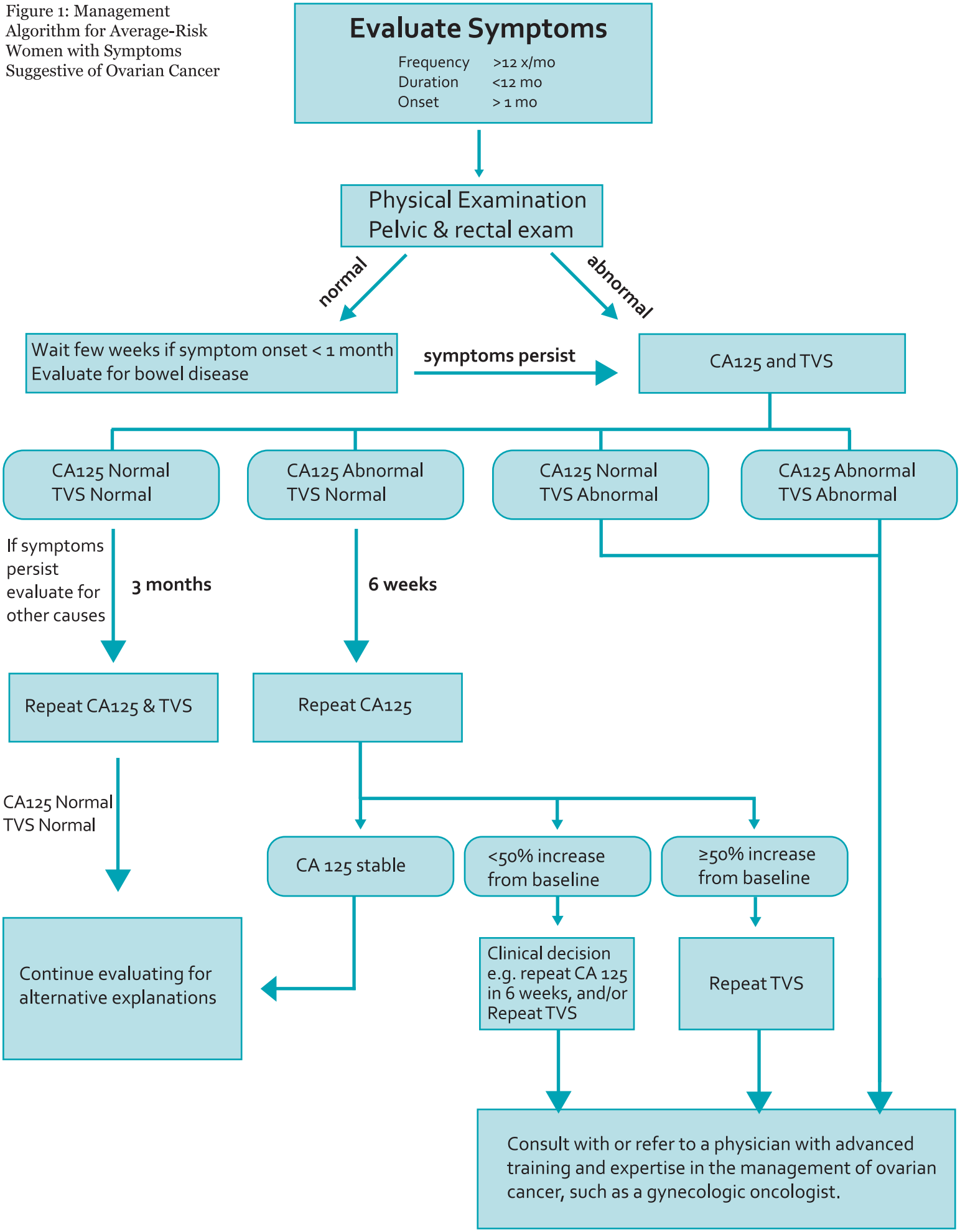
There are not presently sufficient data about the effect of intervention based on symptoms to know if any survival benefit will accrue to women found to have ovarian cancer. The purpose of making recommendations in the absence of such data is to attempt to provide the best available expert advice to the practitioners who are now responsible for conducting the evaluations recommended by the previous statement on ovarian cancer symptoms.[8]

Management Strategies

The management strategies are summarized in Figure 1. These strategies are for individuals who are at average risk for ovarian cancer. Women with a strong family history of breast and ovarian cancer or of a high-risk genetic syndrome and who have symptoms suggestive of ovarian cancer should follow existing guidelines for women at high risk.[10-12]

Figure 1: Management Algorithm for Average-Risk Women with Symptoms Suggestive of Ovarian Cancer

Figure 1: Management Algorithm for Average-Risk Women with Symptoms Suggestive of Ovarian Cancer



Women who experience bloating, pelvic or abdominal pain, difficulty eating or feeling full quickly, and/or urinary urgency or frequency more often than 12 times per month, for at least one month and less than 12 months, and whose symptoms are otherwise unexplained should see their physician and undergo a complete examination. If a complete and thorough examination, including a pelvic and rectal examination, is normal and the symptoms are of recent onset, i.e. about one month, it is reasonable to wait a few additional weeks to see if the symptoms persist. If the physical examination is normal but symptoms still persist, CA-125 testing and transvaginal sonography should be performed, as described in Figure 1. It should be noted, however, that pelvic exams have a low sensitivity for detecting masses even under optimal circumstances.[13] Nevertheless, many women who have ovarian cancer will not experience symptoms until their tumor is at stage 3, and many of these women will not have had a recent pelvic exam. The exam sensitivity is higher for advanced stage tumors. Evaluation for IBS or other bowel disease should also be considered at this time if not previously done.

If there is a palpable abnormality in the anatomy of the pelvis and its content, or evidence of an otherwise unexplained mass, then the woman should have CA-125 testing and transvaginal ultrasound (TVS) to evaluate the ovaries and fallopian tubes.[14]

Research indicates that symptoms that have been present for more than a year are less likely to represent ovarian cancer than those of recent onset, and abnormal test results in women with symptoms of long standing are more likely to be false positives than in women with onset of symptoms within 6-12 months.[6] However, evaluation for ovarian cancer is appropriate for women whose symptoms have been present for more than 12 months if not done previously.

Transvaginal Ultrasound

TVS should be performed by a sonographer who has extensive experience in the evaluation of ovarian size and morphology. The American Institute of Ultrasound in Medicine training guidelines suggest that a minimum of 170 examinations is required for proficiency.15 Some experts recommend a minimum of 400-500 examinations to gain the requisite experience.[16](Jack van Nagell, personal communication)

The definition of an abnormal sonogram is important. In one widely used ovarian cancer screening algorithm, the two criteria used for abnormality are volume and morphology.[17] The ovarian volume is calculated using the prolate ellipsoid formula (L x H x W x 0.523). A value of >10 cm3 in postmenopausal women or of >20 cm3 in premenopausal women is >2 standard deviations above the mean normal ovarian volume and therefore abnormal.[18]

The second criterion for abnormality is ovarian morphology. Ovarian tumors are morphologically classified as solid, cystic, or complex (containing both solid and cystic components). The vast majority of primary ovarian cancers detected by TVS are complex.[17] Patients with unilocular cystic ovarian masses with a diameter of <5 cm are at very low risk for cancer.[17] In one reported series, 3,000 women with unilocular cystic tumors were followed sonographically for at least 6 years, and none developed ovarian cancer.[19] Therefore, unilocular cystic ovarian tumors <5 cm in diameter should not be considered in the abnormal category. However, in complex ovarian tumors, volume is associated directly with risk of malignancy[20] and the definition for abnormal volume in these tumors should be utilized. An ultrasound report should state clearly whether the ovary is normal or abnormal; “borderline” is not acceptable, and a statement should include the probability of a cancer in complex cysts or a solid mass, especially for premenopausal women.

CA-125

Table 1 presents specific recommendations for the management of symptomatic women based on their menopausal status and their test results. While 35U/mL is widely used as the cut-off value for

both pre- and post-menopausal women, the false-positive rate for CA-125 testing is higher among pre-menopausal women.[21] In order to achieve a false-positive rate equivalent to that in post-menopausal women, i.e. 2%, the cut-off value for pre-menopausal women would be approximately 53U/mL.(Steven Skates and Bob Bast, personal communication)

Table 1: Management Strategies Based on CA-125 and TVS Results

CA-125 Normal, TVS Normal	Evaluate other causes of symptoms Consider repeat CA-125 and TVS if symptoms persist after 3 months
CA-125 Abnormal, TVS Normal	Repeat CA-125 in 6 weeks
CA-125 Normal, TVS Abnormal	Consult with or refer to a physician with advanced training and expertise in the management of ovarian cancer, such as a gynecologic oncologist, for evaluation for possible repeat imaging or surgery
CA-125 Abnormal, TVS Abnormal	Consult with or refer to a physician with advanced training and expertise in the management of ovarian cancer, such as a gynecologic oncologist, for surgical consultation

Normal CA-125 is defined as ≤53U/mL in Premenopausal Women and ≤35U/mL Postmenopausal Women
Abnormal CA-125 is defined as >53U/mL in Premenopausal Women and >35U/mL in Postmenopausal Women
Some laboratories use their own tests which may have different cut-off values; cut-off values need to be adjusted for the laboratory.

If TVS is normal and CA-125 is elevated, repeat CA-125 testing should be done at 6 weeks so that the patient, if pre-menopausal, will be at a different phase of the menstrual cycle. If CA-125 is repeated in 6 weeks then a method is required for evaluating the change over time, with the possibility of additional CA-125 results having to be interpreted. Research is underway to develop optimal methods for interpreting multiple CA-125 values over time.[22] We offer the following guidance, which is subject to revision, and not meant to be regarded as validated protocols. The CA-125 is repeated at six weeks if the first test is elevated and the ultrasound is normal. If the CA-125 level on the second test rises 50% or more from the baseline test, then repeat ultrasound is recommended. If the CA-125 value is stable, then the patient would follow the same path as if the first set of tests had normal CA-125 and ultrasound test results. If the CA-125 is rising but less than 50%, then a clinical decision is required, which may include returning in six additional weeks for another CA-125 test and/or repeat ultrasound.

If all exams are normal but symptoms persist and have not been explained by another potential diagnosis, testing should be repeated in 3 months. If both tests are again normal, continue evaluating for alternative explanations or differential diagnosis.

If either the TVS or the CA-125 is abnormal, or if both tests are abnormal, consultation with or referral to a physician with advanced training and expertise in the management of ovarian cancer, such as a gynecologic oncologist, is recommended.

Limitations and Potential Harms

To date, screening of high-risk populations has not been reliably associated with detection of disease at early stages[23-27] although annual TVS screening of asymptomatic women was associated with earlier stage diagnosis in two large studies. [17, 28] The potential for morbidity associated with excessive testing,

false positives, and avoidable surgery is recognized. In the UK collaborative Trial of Ovarian Cancer Screening, for example, 2.9% of women who underwent surgery and were found to have benign pathology or normal ovaries experienced a major complication.[28] Even under the most conservative assumptions, most patients with abnormal test results will not have ovarian cancer, although many will have other ovarian pathology.

There are concerns about the costs of implementing these recommendations as well as the limited capacity and access to high-quality TVS by sonographers experienced with evaluation of the ovaries for non-obstetric purposes.

Conclusion

Evidence is currently incomplete regarding the appropriate management of women who present with frequent, unexplained symptoms of recent onset that are suggestive of ovarian cancer. Nevertheless, the identification and subsequent public awareness of the association of these symptoms with ovarian cancer requires guidance to clinicians. As awareness increases, more women will seek medical evaluation. Given the low prevalence of the disease and the lack of specificity of the symptoms, in most cases these women will not have ovarian cancer. For the small number that will be diagnosed, it remains to be determined if these recommendations will impact stage of diagnosis or mortality. Nevertheless, the possibility of ovarian cancer exists and the patient should be evaluated.

These management strategies represent the expert opinion of individuals with experience in the detection of ovarian cancer regarding the use of CA-125 and transvaginal ultrasound to diagnose ovarian cancer in symptomatic women. Currently there are several investigations attempting to identify early detection strategies that exploit molecular markers of cancerous and normal tissue. Until studies lead to the development of a validated and acceptable serum or molecular early detection tool, it is reasonable to be alert to the onset of the otherwise unexplained symptom complexes. Women will need to be informed about the benefits, limitations, and potential harms of ovarian cancer detection tests and diagnostic procedures, including the likelihood of false-positive findings.

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