Endometrial Cancer

Endometrial carcinoma is the most commonly diagnosed gynecologic malignancy; almost every gynecologist will encounter it. A thorough understanding of the epidemiology, pathophysiology, and diagnostic and management strategies for this type of cancer allows the obstetrician–gynecologist to identify women at increased risk, contribute toward risk reduction, and facilitate early diagnosis. The purpose of this document is to review the current understanding of endometrial cancer and to provide guidelines for management that have been validated by appropriately conducted outcome-based research when available. Additional guidelines on the basis of consensus and expert opinion also are presented.

Background

Epidemiology

In the United States, endometrial cancer will be diagnosed in an estimated 54,870 women in 2015, with 10,170 succumbing to the disease (1). More than 70% of cases of endometrial cancer are stage I at the time of diagnosis, when the reported 5-year survival rate is 90% (2). The mean age of diagnosis in the United States is 63 years (3). Caucasian women have a 2.81% lifetime risk of developing uterine cancer compared with a 2.48% lifetime risk for African American women (4). African American women are more likely to have nonendometrioid, high-grade tumors (known as type II), which are associated with a more advanced stage of disease (stage III and stage IV) at the time of diagnosis, compared with Caucasian women who have similar demographic characteristics (5).

Classification and Histopathology

Endometrial cancer can be categorized broadly into two types that differ in epidemiology, genetics, prognosis, and even treatment: 1) type I, or endometrioid adenocarcinoma, is the most common histologic type of endometrial cancer and accounts for more than three fourths of all cases, and 2) type II is characterized by clear cell and papillary serous tumor histologies. Most cases of type I cancer are low grade and confined to the uterus when diagnosed (2). The precursor lesion of type I endometrioid adenocarcinoma is endometrial intraepithelial neoplasia (also known as atypical endometrial hyperplasia). There are currently two systems of endometrial precancer nomenclature in common usage: 1) the World Health Organization 1994 schema, which includes the “atypical endometrial hyperplasia” designation, and 2) the endometrial intraepithelial neoplasia diagnostic schema developed by the International Endometrial Collaborative Group (6). The endometrial intraepithelial neoplasia schema is increasingly viewed as preferable because it more clearly distinguishes between clinicopathologic entities that are managed differently. When endometrial intraepithelial neoplasia is absent, the risk of progression to endometrioid carcinoma ranges from 1% to 8%, depending on the degree of architectural complexity (7). More contemporary data demonstrated a 4.6% (95% confidence interval [CI], 3.3–5.8%) 19-year cumulative
risk of carcinoma among women with nonatypical endometrial hyperplasia (8). Endometrial intraepithelial neoplasia, however, is much more likely to progress to cancer and may be found coexisting with an undiagnosed endometrioid carcinoma in 30–50% of cases (9, 10). In a prospective trial conducted by the Gynecologic Oncology Group (GOG), 306 women in whom endometrial intraepithelial neoplasia was diagnosed on preoperative biopsy underwent hysterectomy without first receiving medical treatment (9). On final pathology, 42.6% of the women were found to have invasive cancer. Although most of the identified cases of endometrial cancer were minimally invasive grade 1 tumors, 11% of the cases of endometrial cancer demonstrated deep myometrial invasion (9). When endometrial intraepithelial neoplasia is treated conservatively, the 19-year cumulative risk of developing endometrial carcinoma is reported to be 27.5% (95% CI, 8.6–42.5%) (8).

Type II cancer is considered to be high grade and to have a significant risk of extrauterine disease and a poorer prognosis than type I cancer. Uterine papillary serous carcinoma accounts for only approximately 10% of all cases of uterine cancer, but it is responsible for the deaths of almost 40% of patients with endometrial cancer (11). The precursor lesion is thought to be endometrial intraepithelial carcinoma (12, 13). Serous endometrial intraepithelial carcinoma may be associated with an extrauterine tumor at the time of diagnosis and with risk of recurrence, spread, and eventual death from the tumor (14). Clear cell histology also is rare but is associated with a similarly poor prognosis (15). Carcinosarcoma, also known as malignant mixed müllarian tumor of the uterus, is another histologic cell type with a poor prognosis and may represent a subset of adenocarcinoma.

**Risk Factors**

Some of the more common risk factors for type I endometrial cancer are discussed in this section. Additional risk factors for type I endometrial cancer are listed in Table 1.

**Unopposed Estrogen**

Prolonged exposure to unopposed estrogen, whether endogenous or exogenous, is associated with most cases of type I endometrial cancer. Unopposed endogenous estrogen exposure occurs in chronic anovulation (eg, polycystic ovary syndrome), with estrogen-producing tumors, and with excessive peripheral conversion of androgens to estrone in adipose tissue. Obesity is associated with an increased incidence of endometrial cancer (16). Case-control studies have demonstrated a 200–400% linear increase in risk of endometrial cancer in individuals with body mass index (BMI [calculated as weight in kilograms divided by height in meters squared]) values higher than 25 (17). A meta-analysis that evaluated women taking hormone therapy (HT) showed that BMI is strongly associated with an increased risk of endometrial cancer, with the association becoming stronger at BMI values greater than 27 and being particularly strong in women who have never been exposed to HT (18). Type 2 diabetes mellitus and hypertension are associated with an increased risk of endometrial cancer that may be related to concurrent obesity (19, 20), although an independent association between diabetes and endometrial cancer has been reported (21).

Systemic unopposed estrogen therapy increases the risk of endometrial cancer by up to 20-fold, with the increasing risk correlating with the duration of use (22–26). Concomitant progestin administration mitigates this risk. When progestins are administered continuously, intermittently (at least 10 d/mo), or through a

### Table 1. Risk Factors for Type I Uterine Corpus Cancer

<table>
<thead>
<tr>
<th>Factors Influencing Risk</th>
<th>Estimated Relative Risk*</th>
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<tbody>
<tr>
<td>Older age</td>
<td>2–3</td>
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<tr>
<td>Residency in North America or Northern Europe</td>
<td>3–18</td>
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<tr>
<td>Higher level of education or income</td>
<td>1.5–2</td>
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<tr>
<td>White race</td>
<td>2</td>
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<tr>
<td>Nulliparity</td>
<td>3</td>
</tr>
<tr>
<td>History of infertility</td>
<td>2–3</td>
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<tr>
<td>Menstrual irregularities</td>
<td>1.5</td>
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<tr>
<td>Late age at natural menopause</td>
<td>2–3</td>
</tr>
<tr>
<td>Early age at menarche</td>
<td>1.5–2</td>
</tr>
<tr>
<td>Long-term use of unopposed estrogen</td>
<td>10–20</td>
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<tr>
<td>Tamoxifen use</td>
<td>2–3¹</td>
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<tr>
<td>Obesity</td>
<td>2–5</td>
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<tr>
<td>Estrogen-producing tumor</td>
<td>&gt;5</td>
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<tr>
<td>History of type 2 diabetes, hypertension, gallbladder disease, or thyroid disease</td>
<td>1.3–3</td>
</tr>
<tr>
<td>Lynch syndrome</td>
<td>6–20²</td>
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*Relative risks depend on the study and referent group employed.


levonorgestrel-releasing intrauterine system (levonorgestrel intrauterine device [IUD]), the risk is reduced to below that of women not receiving HT (27–31). However, the use of estrogen along with a 10–14-day progestin course once every 3 months was significantly associated with an elevated risk of developing endometrial carcinoma for exposures of 5 years or more (odds ratio, 1.63; 95% CI, 1.12–2.38) and showed a tendency toward an elevated risk for exposures of less than 5 years, although this association was not statistically significant (odds ratio, 1.40; 95% CI, 0.82–2.38) (31). Given the variable response to HT and the associated risks, it is recommended that health care providers individualize care and treat women with the lowest effective dose for the shortest duration that is needed to relieve vasomotor symptoms. The decision to continue HT should be individualized and based on a woman’s symptoms and the risk–benefit ratio, regardless of age (32).

**Selective Estrogen Receptor Modulators**

A number of selective estrogen receptor modulators are available and vary in the degree to which they act as estrogen agonists in endometrial tissue. Although the use of tamoxifen significantly reduces the risk of breast cancer and breast cancer recurrence, its use is associated with an increase in the incidence of endometrial cancer (Table 1) (33–36). However, the ability of tamoxifen to induce endometrial malignancy and other histopathologic conditions appears to differ between premenopausal and postmenopausal women (36). In the National Surgical Adjuvant Breast and Bowel Project prevention trial of high-risk women, there was no statistically significant difference in endometrial cancer rates between women treated with tamoxifen and those in the placebo group in women 49 years and younger; however, in women 50 years and older, the risk ratio was 4.01 (95% CI, 1.70–10.90) for those treated with tamoxifen versus those receiving placebo (37). Raloxifene, which also is used to reduce the risk of breast cancer and breast cancer recurrence, does not increase the risk of endometrial cancer or uterine bleeding (38). Ospemifene, which is approved for the treatment of moderate-to-severe dyspareunia, has only limited long-term safety data. Among 180 women who were treated with ospemifene for 52 weeks, no cases of endometrial hyperplasia or endometrial carcinoma were identified, although there was a dose-related mean increase in endometrial thickness: 0.68 mm (30 mg/d) and 1.14 mm (60 mg/d) (39).

**Age**

Age also represents an important risk factor for the development of endometrial cancer. Most women are diagnosed after menopause, with only 15% diagnosed before age 50 years and only 5% before age 40 years (40). Younger women who develop endometrial cancer are more likely to be obese and nulliparous and to have well-differentiated endometrioid histology and a lower-stage disease (41, 42). The most common risk factors for the development of endometrial cancer in young women are increasing BMI, nulliparity, and irregular menstrual cycles (42). The risk of endometrial cancer may be increased by as much as 22-fold in women younger than 45 years whose BMIs are greater than 35 (43). Type II endometrial cancer is more common in older, nonwhite, multiparous women and current smokers (44).

**Reproductive Characteristics**

Reproductive characteristics associated with an increased risk of endometrial cancer include nulliparity, infertility, early age of menarche, and late age of menopause (45, 46). The use of combination oral contraceptive pills, depot medroxyprogesterone acetate, and the levonorgestrel IUD all decrease the risk of developing endometrial cancer (47–49). Data are less clear regarding the risk of endometrial cancer associated with copper IUD use, with two studies demonstrating a decrease in risk and one study demonstrating no effect (50).

**Smoking**

Smoking has been associated with a decreased risk of type I endometrial cancer, especially in postmenopausal women (51). However, smoking has been associated with an increased risk of type II endometrial cancer (44).

**Genetic Predisposition**

Women with Lynch syndrome (formerly known as hereditary nonpolyposis colorectal cancer) are at an increased risk of developing colon cancer, ovarian cancer, and type I endometrial cancer. This autosomal dominant syndrome is characterized by a germline mutation in one of the mismatch repair genes, typically MLH1, MSH2, PMS2, or MSH6. The estimated cumulative risk of developing endometrial cancer by age 70 years ranges from 16% to 61% depending on the individual genetic mutation (52). Almost 10% of the women in whom endometrial cancer is diagnosed before age 50 years have an underlying diagnosis of Lynch syndrome (53). This risk of endometrial cancer increases significantly after age 40 years, with a mean age of diagnosis of 48–50 years in women with a genetic predisposition. There is controversy in the literature regarding whether young women with endometrial cancer have an increased rate of Lynch mutations. Therefore, it is reasonable to triage women with endometrial cancer for genetic risk assessment by
using the 2004 Bethesda criteria guidelines modified to include endometrial cancer as a sentinel cancer (54, 55).

Cowden disease, a rare autosomal dominant familial cancer susceptibility syndrome characterized by germ-line PTEN mutations, is associated with an increased risk of breast cancer, thyroid cancer, and endometrial cancer (56). The association between germ-line mutations in BRCA genes and the risk of endometrial cancer remains controversial (57, 58). Results from some studies have suggested that an increased risk of endometrial cancer in BRCA mutation carriers may not be due to the mutation per se, but rather to prophylaxis or treatment with tamoxifen (59, 60). Thus, for women with BRCA1 or BRCA2 mutations who take tamoxifen, hysterectomy may be considered to reduce the risk of endometrial cancer (59–61).

Clinical Presentation

The most common symptoms of endometrial cancer are abnormal uterine bleeding (including irregular menses and intermenstrual bleeding) and postmenopausal bleeding. Patients who have advanced disease may have symptoms similar to those seen with advanced ovarian cancer, such as abdominal or pelvic pain, abdominal distention, bloating, early satiety, and change in bowel or bladder function. At present, there is no available recommended routine screening test to identify endometrial cancer.

Surgical Staging

Comprehensive surgical staging of endometrial cancer involves removing the uterus, cervix, adnexa, and pelvic and para-aortic lymph node tissues as well as obtaining pelvic washings. Pelvic lymphadenectomy typically is defined as removal of the nodal tissue from the distal half of the common iliac arteries, the anterior and medial aspect of the external iliac artery and vein down to the point at which the deep circumflex iliac vein crosses the external iliac artery, and the obturator fat pad anterior to the obturator nerve. Para-aortic lymph node dissection is defined as removal of nodal tissue over the distal inferior vena cava from the level of the inferior mesenteric artery to the midleft common iliac artery.

Adequate nodal dissection requires that lymphatic tissue be demonstrated pathologically from each side (right and left), but no minimum nodal counts have been established. Thus, some practitioners may choose selective lymph node sampling rather than full dissection. Retrospective data suggest that patients who undergo multiple site sampling have improved survival rates over those who have limited sampling or no sampling performed (62, 63). The caveat to nodal sampling rather than full dissection is that inspection or palpation of lymph nodes has not been shown to be a sensitive method for detecting positive lymph nodes, with fewer than 10% of patients with lymph node metastases having grossly enlarged lymph nodes (64).

Despite these well-defined criteria for surgical staging, surgeons still debate the extent of lymphadenectomy that is necessary. Particular controversy surrounds the need for and the extent of para-aortic lymph node dissection in all patients. When lymph nodes are involved in a case of metastatic endometrial cancer, the para-aortic lymph nodes will be involved 57–67% of the time (65, 66). Isolated para-aortic lymph node involvement in the absence of pelvic lymph node metastases, however, occurs in only 16–17% of patients with lymph node involvement (65, 66). Therefore, depending on the patient populations chosen for lymphadenectomy, the risk of isolated para-aortic lymph node metastases ranges from 1% to 3.5% (65, 67). Some authors recommend that a limited inframesenteric para-aortic lymphadenectomy be performed on all patients undergoing pelvic lymphadenectomy (68, 69), whereas others suggest that para-aortic lymph node dissection may be warranted only in those patients with high-risk pathology. One prospective study reported that patients with low-grade disease (i.e., grade 1 or grade 2 endometrioid lesions with less than 50% myometrial invasion and tumor size of 2 cm or less) seem to be at low risk of lymph node metastases and may not require a systematic lymphadenectomy; however, this study was dependent on extensive intraoperative frozen section evaluation, which may not be reproducible in most hospitals (65).

Clinical Considerations and Recommendations

► How is endometrial cancer diagnosed?

The evaluation of premenopausal women with abnormal uterine bleeding includes a thorough medical history and physical examination, appropriate laboratory and imaging tests, and consideration of age-related factors (70). The literature is unclear about when evaluation with imaging is indicated in premenopausal women with abnormal uterine bleeding. Ultrasound measurement of endometrial thickness in premenopausal women has no diagnostic value and should not be performed. The decision to histologically evaluate the endometrium should be based on symptomatology and clinical presentation.

Any vaginal bleeding in a postmenopausal woman requires assessment to exclude malignancy. Women with
postmenopausal uterine bleeding may be assessed initially with either endometrial biopsy or transvaginal ultrasonography; this initial evaluation does not require performance of both tests (71). Among postmenopausal women who experience uterine bleeding, pelvic ultrasonography and endometrial sampling have shown efficacy. A review of data from approximately 2,900 postmenopausal women collected from 13 published studies demonstrated that an endometrial thickness of 5 mm or less found by ultrasonography resulted in a sensitivity of 90% and a specificity of 54% for the detection of endometrial cancer (72). This compares to 98% and 35%, respectively, when the cutoff was reduced to 3 mm. When transvaginal ultrasonography is performed for the initial evaluation of patients with postmenopausal bleeding and an endometrial thickness of less than or equal to 4 mm is found, endometrial sampling is not required (71). Endometrial thickness of greater than 4 mm in a patient with postmenopausal bleeding should trigger alternative evaluation (such as sonohysterography, office hysteroscopy, or endometrial biopsy), as should an inability to adequately visualize thickness (71).

Classically, dilation and curettage (D&C) has been the procedure used to diagnose endometrial cancer. However, outpatient endometrial sampling with disposable devices is reliable and accurate for the detection of disease in most cases of endometrial cancer and has become the method of choice for histologic evaluation of the endometrium. A meta-analysis of studies on the efficacy of several devices for endometrial sampling indicated that all devices analyzed had a specificity rate of 98% (73). If a surgical approach is favored, D&C with hysteroscopic guidance is recommended over D&C alone because it has higher accuracy and superior diagnostic yield (74, 75). Hysteroscopy, although not required, is recommended with directed D&C to include any discrete lesions as well as the background endometrium. This combination will provide the best opportunity to confirm the diagnosis of a true premalignant endometrial lesion and exclude an associated endometrial carcinoma.

Because rare cases of endometrial carcinoma (particularly type II) can present with an endometrial thickness of less than 3 mm, persistent or recurrent uterine bleeding should prompt a histologic evaluation of the endometrium regardless of endometrial thickness. The approach should be dictated by the order of investigative evaluation. For example, if the initial assessment involved only pelvic ultrasonography, endometrial sampling should be performed. Similarly, if office endometrial sampling has already been performed and has demonstrated no evidence of hyperplasia or malignancy, hysteroscopy with D&C is recommended (76–78).

Is a metastatic evaluation necessary in women with newly diagnosed endometrial cancer?

Endometrial cancer is a surgically staged disease, with most patients having disease confined to the uterus. Therefore, routine preoperative assessment of patients with endometrial cancer with imaging tests that evaluate for metastasis is not necessary. However, preoperative assessment of metastatic disease with imaging (computed tomography [CT], magnetic resonance imaging [MRI], or positron emission tomography [PET]/CT), measurement of serum CA 125, or both may be clinically important under special circumstances, such as when the patient is a poor surgical candidate because of medical comorbidities; when symptoms suggest possible metastasis to unusual sites, such as bones or the central nervous system; and when preoperative histology demonstrates a high-grade carcinoma (including grade 3 endometrioid, papillary serous, clear cell, and carcinosarcoma) (79–83).

What role does a gynecologic oncologist play in the initial management of endometrial cancer?

Total hysterectomy with bilateral salpingo-oophorectomy (BSO)—involving removal of the cervix, uterus, fallopian tubes, and ovaries—used to be the mainstay of treatment for uterine cancer. In 1988, however, with mounting evidence that extraperitoneal disease was associated with poor outcomes and that patients with advanced disease required more than just surgical intervention, corpus cancer was converted to a surgically staged disease. Although opinion as to the role of routine lymphadenectomy remains divided, relative consensus has been reached that the information gained by comprehensive surgical staging, including lymphadenectomy, offers prognostic pathologic findings that can be used to individualize additional treatment (84). Patients with low-grade, minimally invasive disease do not clearly benefit from comprehensive staging, but no true and reliable preoperative predictive model accurately identifies such individuals. Additionally, intraoperative decisions about the need for comprehensive staging are hindered by the difficulty of ensuring broad institutional intraoperative assessment that is reproducible and reliable. Physicians with advanced training and expertise in the treatment of women with endometrial cancer, such as gynecologic oncologists, understand the nuances of uterine cancer management, including the selection and sequencing of treatment modalities likely to benefit the individual patient. Patient outcomes are improved when high-volume surgeons in high-volume institutions render care, and this outcomes

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model typically is reproduced by standard gynecologic oncology practice (85). When it is practical and feasible, preoperative consultation with a physician with advanced training and demonstrated competence in the treatment of endometrial cancer, such as a gynecologic oncologist, is recommended. Such involvement improves the preoperative and intraoperative decision process, allows completion of any necessary procedure (comprehensive staging or debulking), facilitates decision making regarding the need for additional therapy, and results in a comprehensive and cost-effective clinical approach. Consultation may be particularly beneficial in the following situations:

- The option to completely and adequately surgically stage the patient is not readily available at the time of her initial procedure.
- Preoperative histology (grade 3, papillary serous, clear cell, carcinosarcoma) suggests a high risk of extraterine spread.
- The final pathology test result reveals an unexpected endometrial cancer after hysterectomy performed for other indications.
- There is evidence of cervical or extraterine disease, including lymph node or ovarian metastases.
- Recurrent disease is diagnosed or suspected.
- Nonoperative therapy is contemplated.

What are the advantages and potential complications of comprehensive staging?

The advantages of comprehensive surgical staging lie in diagnosis, prognosis, and proper triage of patients for adjuvant therapy. The International Federation of Gynecology and Obstetrics’ (FIGO’s) surgical staging system for endometrial cancer is based on surgical pathology, and comprehensive staging allows for accurate definition of disease extent (Box 1). In the GOG-33 study, investigators found that 9% of patients with clinically determined stage I disease had pelvic nodal metastases, 6% had para-aortic nodal metastases, 5% had disease that had spread to the adnexa, and 6% had other extraterine metastases at the time of surgery (64). These patients with more advanced-stage disease have poorer prognoses and require additional therapy, which may not be recognized without comprehensive surgical staging.

When comprehensive surgical staging has identified stage I disease, pathologic findings of the hysterectomy specimen and patient factors can identify patients who might benefit from further treatment. The GOG-99 study defined a high-intermediate risk group of patients based on age and pathologic factors, including tumor grade (grade 2 and grade 3), depth of myometrial invasion (outer third), and lymphovascular space invasion. Radiation therapy in these patients results in improved progression-free survival and fewer local recurrences (86). Alternatively, those patients with stage I disease who do not have high-intermediate risk factors can be identified and overtreatment can be avoided, sparing them from potential complications of radiation therapy. Despite these benefits, no randomized trials have demonstrated a benefit of lymphadenectomy in apparent early-stage endometrial cancer (disease confined to the uterine corpus or cervix [stage I and stage II]). However, available trials (87, 88) have
been criticized for a number of methodological flaws that limit their validity.

Comprehensive surgical staging is associated with inherent risks. Potential complications include injury to major vessels or nerves, lymphedema, and associated cellulitis. Lymphedema can have an adverse effect on quality of life (89). The exact incidence of lymphedema is unknown, but a recent study reported its occurrence in 47% of patients who underwent lymphadenectomy (89). The GOG currently is undertaking a prospective evaluation of the true incidence of lymphedema. Negative effects can be avoided by limiting the pelvic lymphadenectomy to the region cephalad to the deep circumflex iliac vein, avoiding removal of the circumflex iliac nodes distal to the external iliac nodes (90, 91). Lymphadenectomy may alter or eliminate the need for adjuvant therapy and its associated morbidity.

What is the recommended initial surgical approach for endometrial cancer?

The initial management of endometrial cancer should include comprehensive surgical staging (total hysterectomy, BSO, pelvic and para-aortic lymphadenectomy, and the collection of peritoneal cytology [pelvic washings]). Exceptions to this approach should be made only after consultation with a practitioner specializing in the treatment of endometrial cancer, such as a gynecologic oncologist.

Laparotomy and Minimally Invasive Surgical Approaches

Traditionally, surgical staging for endometrial cancer was accomplished with open laparotomy. Subsequent randomized, controlled trials have compared laparotomy with laparoscopy (92–94). In the GOG LAP2 study, 2,616 women with endometrial cancer were randomized in a 2:1 fashion to undergo either laparoscopy or laparotomy for comprehensive surgical staging (94). Conversion from laparoscopy to laparotomy occurred in 25.8% of cases, primarily because of poor exposure, and was dependent on BMI (17.5% among patients with a BMI of 25 or less, 26.5% among patients with a BMI of 34–35, and 57.1% among patients with a BMI greater than 40) (94). Laparoscopy was associated with fewer moderate-to-severe postoperative adverse events than laparotomy (14% versus 21%; \( P < 0.001 \)) and similar rates of intraoperative complications. Although operative time was longer for laparoscopy, the incidence of hospitalization longer than 2 days was significantly lower compared with laparotomy (52% versus 94%; \( P < 0.001 \)). Laparoscopy patients reported higher quality of life during the recovery period compared with laparotomy patients (93, 94). In a follow-up study, the estimated hazard ratio for rate of recurrence for laparoscopy relative to laparotomy at 3 years was 1.14 (90% lower bound, 0.92; 95% upper bound, 1.46), falling short of the protocol-specified definition of noninferiority (95). However, the estimated 5-year overall survival rate was almost identical in both groups at 89.8%. A meta-analysis of survival data from three smaller randomized trials did not detect a survival difference between the surgical approaches (96, 97).

Minimally invasive surgical technologies continue to evolve. Compared with traditional laparoscopy, robotic-assisted laparoscopy appears to have a shorter learning curve and similar benefits (98). Although robotic-assisted laparoscopy has not been compared prospectively with conventional laparoscopy in a randomized trial, complication rates, conversion rates, and length of hospital stay appear similar, and estimated blood loss appears lower with the robotic approach (99–101). Several cost comparisons between surgical approaches used for the management of endometrial cancer have been published (102–104). Although traditional laparoscopy typically is the least expensive surgical approach, robotic-assisted laparoscopy appears to be less costly than laparotomy, especially when societal costs associated with recovery are considered. Minimally invasive surgery should be embraced as the standard surgical approach for comprehensive surgical staging in women with endometrial cancer. However, power morcellation should not be used in women with known or strongly suspected uterine malignancy (105). Robotic-assisted laparoscopic staging is a feasible and safe alternative to traditional laparoscopy in women with endometrial cancer.

Vaginal Approach

Although a vaginal approach is the preferred surgical approach for hysterectomy in women with benign disease, it precludes the thorough abdominal survey and lymphadenectomy that is recommended in the management of endometrial cancer (106). For women who are elderly, are obese, or have extensive comorbid conditions, the risks associated with surgical staging via an abdominal or laparoscopic approach may outweigh the potential benefits. Several authors have reported on vaginal hysterectomy for treatment of early-stage endometrial cancer in select women at high surgical risk (107–111). Many of the studies report similar survival rates in women who underwent vaginal hysterectomy and those in whom the abdominal approach was used (109–111). Therefore, vaginal hysterectomy may be an appropriate treatment for early-stage endometrioid endometrial cancer in select patients who are at high risk of surgical morbidity.
Is there a role for adjuvant therapy in patients with stage I or stage II endometrial cancer?

Selecting appropriate adjuvant therapy for patients with early-stage endometrial cancer is difficult. To date, no level I evidence supports an overall survival advantage for adjuvant therapy of any form in patients with early-stage endometrial cancer. Further complicating the decision process is the fact that patients with “early-stage” endometrial cancer actually comprise two types of patients: 1) those who are comprehensively staged and have received appropriate nodal evaluation and 2) those who are not comprehensively staged.

The value of adjuvant radiation therapy in comprehensively staged patients who have risk factors associated with disease relapse remains unclear. Several randomized trials have demonstrated that adjuvant radiation for certain stage I or stage II endometrial carcinomas reduces the local recurrence rate but does not affect overall survival (86, 112–115). A high-intermediate risk group has been defined, however, in which adjuvant radiation therapy improves progression-free survival and decreases the risk of local recurrence (86). The following risk factors were found to be associated with an increased rate of recurrence: grade 2 or grade 3 disease, the presence of lymphovascular space invasion, and outer-third myometrial invasion. The high-intermediate risk group included women 70 years or older with one of these risk factors, women 50 years or older with two of these risk factors, and women of any age with all of these risk factors (86). Conclusions from these trials are limited, however, because of differences in inclusion criteria and the allowance of vaginal brachytherapy in the control groups. Among patients who have not had radiation therapy, salvage therapy at the time of recurrence is most often curative (116–118).

Vaginal brachytherapy has been shown in one study to be equivalent to whole pelvic irradiation in achieving locoregional control and providing reasonable disease-specific and overall survival in patients with certain high-intermediate risk factors for recurrent endometrial cancer: older than 60 years with stage IB grade 1 or grade 2 disease; older than 60 years with stage IA grade 3 disease with myometrial invasion; or any age with endocervical glandular involvement and disease otherwise confined to the uterus, excluding those with stage IB grade 3 disease (115). These findings apply to all patients regardless of whether they have undergone a comprehensive surgical staging procedure. Vaginal brachytherapy is associated with significantly fewer gastrointestinal toxic effects as well as a better quality of life (115, 119). Thus, vaginal brachytherapy should be the adjuvant treatment of choice over whole pelvic irradiation in certain patients with a high-intermediate risk of recurrent endometrial cancer.

Is there a benefit from cytoreduction in patients with advanced-stage or recurrent endometrial cancer?

Approximately 10–15% of all new cases of endometrial cancer will involve disease that has spread outside the uterus. These cases account for more than 50% of all uterine cancer-related deaths, with survival rates as low as 5–15% (120, 121). These patients are treated with a multimodal approach that includes surgery, chemotherapy, and radiation therapy, with cytoreduction being the most crucial aspect. Optimal surgical cytoreduction (variably defined as less than or equal to 1 cm or 2 cm) has been found to improve progression-free and overall survival rates in patients with advanced-stage or recurrent endometrial cancer.

Five large retrospective studies have addressed the advantages of optimal cytoreductive surgery in patients with stage III and stage IV endometrial adenocarcinoma. Each study demonstrated a statistically significant progression-free and overall survival advantage when optimal cytoreduction was achieved (122–126). All five studies described cytoreduction as an independent prognostic factor for overall survival in the management of patients with advanced-stage endometrial cancer. For those patients in whom the tumor was determined to be unresectable, the median survival was 2–8 months, regardless of further treatment with radiation therapy, chemotherapy, or both (124–126). The extent of residual disease in advanced-stage endometrial cancer appears to have a direct influence on survival. In one study, the median survival for patients who had less than 1-cm residual disease was 15 months, compared with 40 months among those who had microscopic disease (122). In another study, the median survival for patients with no residual disease was 40 months, compared with 19 months for those who had any residual disease (126).

Secondary cytoreductive surgery for recurrent endometrial cancer also has been shown to improve progression-free and overall survival, whether the recurrence is localized to the pelvis or disseminated throughout the abdomen. Among women with recurrent endometrial cancer, survival seems to be dependent on the type of recurrence (solitary recurrence versus carcinomatosis), the ability to achieve optimal cytoreduction, and the time from original treatment to recurrence (127). Median overall survival after secondary cytoreductive surgery ranges from 39 months to 57 months after surgery (122, 127–129). In patients with localized...
recurrence who previously had radiation therapy, pelvic exenteration remains the only curative option, although it is associated with significant postoperative morbidity (60–80%) and even mortality (10–15%) (130, 131).

What is the optimal adjuvant treatment regimen for advanced-stage or recurrent endometrial cancer?

Advanced-stage endometrial cancer is a heterogeneous disease that may present as microscopic or macroscopic lymph node metastasis, intra-abdominal metastasis, or distant inoperable metastasis such as pulmonary metastasis. Most investigators consider patients with these different presentations as one group, despite their very different prognoses. Therefore, defining an optimal treatment regimen is difficult.

Although optimal cytoreductive surgery may have a therapeutic benefit, patients with metastatic disease, even if resected to microscopic residual disease, have a high risk of recurrence and will benefit from adjuvant treatment (132). The use of chemotherapy in the treatment of advanced endometrial cancer improves patient outcomes. Chemotherapy and radiation therapy used in combination may offer superior outcomes compared with single-modality treatment.

Adjuvant pelvic irradiation with or without extended-field radiation in advanced-stage endometrial cancer has been shown to reduce pelvic recurrence significantly. Failures outside the radiation field, however, limit long-term survival. In 2006, GOG reported a randomized trial comparing whole-abdomen irradiation and chemotherapy with doxorubicin and cisplatin in advanced endometrial cancer (133). The trial demonstrated a survival advantage in the chemotherapy group despite greater toxicity.

Several studies have evaluated the efficacy of combining chemotherapy with radiation therapy. One such study retrospectively evaluated patients with stage IVB endometrial cancers limited to the abdomen and pelvis who underwent cytoreductive surgery followed by adjuvant therapy with platinum-based chemotherapy alone, chemoradiation, or radiation therapy alone (134). There was no difference in survival among the three groups. A randomized trial of radiation therapy followed by one of two chemotherapy regimens in patients with stage III or stage IV disease demonstrated 62–64% recurrence-free survival at 3 years despite 20% of patients not being able to complete therapy, largely because of hematologic toxicity (135). The greatest survival advantage was seen in the subgroup of patients with gross residual disease who received the combination of paclitaxel, doxorubicin, and cisplatin (135). Improved survival with acceptable toxicity has been reported in women with advanced-stage or recurrent endometrial cancer treated with radiation therapy “sandwiched” between rounds of chemotherapy with the combination of carboplatin and docetaxel or paclitaxel. The reported overall 5-year survival rate in the two-case series was 79% (136, 137). Among patients with metastases to the para-aortic lymph nodes, another study reported a 75% 5-year survival rate with the combination of postoperative chemotherapy followed by extended-field (whole-pelvic and para-aortic) radiation therapy (138).

What is the optimal chemotherapy regimen in advanced or recurrent endometrial cancer?

The GOG-177 study compared paclitaxel, doxorubicin, and cisplatin with doxorubicin and cisplatin in 263 chemotherapy-naïve women with measurable FIGO stage III–IV or recurrent endometrial carcinoma of any cell type (139). Response rates as well as overall survival and progression-free survival were significantly better with paclitaxel, doxorubicin, and cisplatin. The paclitaxel, doxorubicin, and cisplatin combination was toxic, however, with 39% of patients experiencing grade 2 or grade 3 peripheral neurotoxicity compared with 5% of patients who received the doxorubicin and cisplatin combination. The most recent GOG study compared paclitaxel, doxorubicin, and cisplatin with paclitaxel and carboplatin. Although this study is closed to accrual, the results are not mature. Two other studies, however, demonstrated significant activity to paclitaxel and carboplatin, similar to that of other regimens, with far less toxicity (140, 141). In women with gross residual disease, chemotherapy with paclitaxel and carboplatin is as effective as other regimens reported in the literature and has less toxicity.

Does hormone therapy have a role in the management of advanced-stage endometrial cancer?

Two phase II GOG studies have addressed the role of hormone therapy in the treatment of advanced or recurrent endometrial cancer. In one study, patients were treated with daily tamoxifen plus alternating weekly cycles of medroxyprogesterone (142). The response rate was 33%, with a median progression-free survival of 3 months and a median overall survival of 13 months. In the other study, patients were treated with alternating 3-week cycles of megestrol acetate and tamoxifen (143). The response rate was 27%, with a median progression-free survival of 2.7 months and a median overall survival of 14 months. Responses in this study occurred in 38% of patients with grade 1 tumors, 24% in those with...
grade 2 tumors, and 22% in those with grade 3 tumors. These results suggest promising activity for hormone therapy for patients with advanced or recurrent endometrial cancer who are unable or unwilling to undergo more aggressive therapies, regardless of tumor grade or hormone receptor status.

What is the recommended evaluation for patients who are considering fertility-sparing treatment for endometrial cancer?

Up to 30% of patients in whom endometrial cancer is diagnosed are younger than 54 years, and approximately 9% of women in whom the disease is diagnosed are younger than 44 years (144–148). Patients considering fertility-sparing options for the treatment of endometrial cancer should be counseled that data on cancer-related and pregnancy-related outcomes are limited. Although the common assumption is that premenopausal women would have early-stage, low-grade malignancies, this may not be the case. In a population-based registry (Geneva Cancer Registry), 3.2% of women with endometrial cancer were 45 years or younger, and only 18% of these women had stage IA, grade 1 endometrial cancer at the time of final surgical pathology (149). Therefore, it is imperative to select carefully those women who may be candidates for fertility-sparing approaches to the management of endometrial cancer (Box 2) (146).

Patients who are considering fertility-sparing treatment should be evaluated with diagnostic modalities aimed at detecting advanced or high-risk disease. For women who wish to pursue fertility-sparing options, D&C may be better at evaluating the tumor grade than office endometrial biopsy. One study showed that only 10% of cases diagnosed by D&C were upgraded at the time of hysterectomy compared with 26% of those diagnosed by endometrial biopsy (150, 151). In addition to higher tumor grade, greater depth of myometrial invasion is associated with an elevated risk of extraterine or nodal metastases. Compared with ultrasonography and CT, MRI may be the preferred modality to evaluate the presence of myometrial invasion (152). Other potentially useful interventions include laparoscopic staging and determination of hormone receptor status (144, 145).

What role do progestins play in the fertility-sparing treatment of endometrial cancer?

Progestins have been the mainstay of conservative hormonal treatment for endometrial cancer in the young woman who wants to preserve fertility and the woman who is deemed to be a poor surgical candidate. The most commonly used progestins are medroxyprogesterone acetate and megestrol acetate (146). Repeat endometrial sampling usually is performed every 3 months in patients while they undergo progestin therapy. In a phase II prospective study, women 40 years or younger who had either endometrial cancer presumed to be confined to the endometrium or endometrial intraepithelial neoplasia were treated with oral medroxyprogesterone acetate for 26 weeks (153). Although the complete response rate was 68%, 47% of those who achieved a complete response subsequently had a recurrence. Most investigators recommend definitive surgical management after the completion of childbearing or if conservative options fail.

When can ovarian preservation be considered in patients with endometrial cancer?

In premenopausal women with endometrial cancer who want to retain ovarian function, ovarian conservation at the time of hysterectomy can be considered, but the decision should be individualized after evaluation of the risk of extrauterine disease and the potential for disease recurrence based on age, histologic cell type, and uterine tumor features.

Traditionally, BSO has been performed routinely in conjunction with hysterectomy when surgically treating women who had endometrial cancer. This recommendation is based on the possibility that the ovaries may be sites of occult metastatic disease and that ovarian estrogen production might lead to an earlier or greater likelihood of recurrence. Investigators examined 175 women with endometrial cancer who did not undergo BSO (154). Their median age was 38.5 years.

<table>
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<th>Box 2. Selection Criteria for Candidates for Conservative Treatment of Endometrial Cancer</th>
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| • A well-differentiated, grade 1, endometrioid endometrial carcinoma  
• No myometrial invasion  
• No extraterine involvement (no synchronous ovarian tumor or metastases, no suspicious retroperitoneal nodes)  
• Strong desire for fertility sparing  
• No contraindications for medical management  
• Patient understands and accepts that data on cancer-related and pregnancy-related outcomes are limited (informed consent) |

and their overall survival rate was 93.3%. All recurrences were seen in women with nonendometrioid histology, deep myometrial invasion, cervical stromal invasion, or inadequate adjuvant therapy. Similarly, an analysis of ovarian preservation at the time of hysterectomy for women with early endometrial cancer using the Surveillance, Epidemiology, and End Results database found no excess deaths associated with ovarian preservation (155). Other studies, however, suggest that the risk of a synchronous ovarian malignancy in premenopausal women with endometrial cancer is as high as 19% and that BSO should be strongly considered (149, 156).

What are the obstetric outcomes in women with endometrial cancer who receive fertility-sparing treatment?

A case series and systematic review of pregnancy after fertility-sparing treatment for endometrial cancer collected data on 50 women and documented 65 deliveries with 77 live births (157). These pregnancies resulted from assisted reproductive technologies and spontaneous conceptions. One maternal death was attributed to recurrent disease. Another group reported an overall pregnancy rate of 35.7%, with approximately 18% of women requiring use of assisted reproductive technologies (146).

What is the appropriate management of incidental diagnosis of endometrial cancer at the time of hysterectomy for another indication?

Women found to have endometrial cancer incidentally after hysterectomy should have their risk of extrauterine disease and potential for disease recurrence evaluated based on age, histologic cell type, and uterine tumor features. Individualized treatment plans can be based on the findings. Treatment decisions with endometrial cancer after hysterectomy are best made in consultation with a specialist with advanced training and demonstrated competence in the treatment of endometrial cancer, such as a gynecologic oncologist.

The need for repeat surgery for the sole purpose of staging in women discovered to have endometrial cancer after hysterectomy needs to be considered carefully. The survival advantages of surgical staging must be weighed against the complications from a second major surgical procedure. Comprehensive pathology review is mandatory to retrieve as much information as possible about the uterine features of the cancer. These features include histologic cell type, nuclear and FIGO grade, depth of myometrial invasion, presence of lymphovascular space invasion, and tumor size. If these uterine features include endometrioid histology, grade 1 or grade 2 tumors, small tumor volume, and superficial or no myometrial invasion, further intervention may not be indicated because these features are compatible with a low risk of extrauterine disease and recurrence (64, 65). Patients who have a higher risk of extrauterine spread or recurrence, such as patients with high-risk histologic cell types, grade 3 tumors, and deep myometrial invasion, should be considered for comprehensive surgical staging. If the patient is a good candidate for surgery, comprehensive staging can be beneficial to help avoid unnecessary adjuvant therapies or to guide such therapies (64, 86, 158, 159).

What is the appropriate follow-up for women after treatment of endometrial cancer?

The aim of surveillance after treatment of endometrial cancer is the detection of treatable recurrent disease, thereby enabling cure or improved survival. A recent review of posttreatment surveillance and diagnosis of recurrence in women with gynecologic cancers sponsored by the Society of Gynecologic Oncology provides comprehensive recommendations and should serve as a primary resource for clinicians (160), along with the guidelines of the National Comprehensive Cancer Network (161). Recommended surveillance after treatment of endometrial cancer includes a follow-up visit every 3–6 months for 2 years, then every 6 months for 3 years, and annually thereafter. Each follow-up visit should include a thorough patient history; elicitation and investigation of any new symptoms associated with recurrence, such as vaginal bleeding, pelvic pain, weight loss, or lethargy; and a thorough speculum, pelvic, and rectovaginal examination (160). Vaginal cytologic evaluation and annual chest radiograph are not recommended because most vaginal recurrences are detected with clinical examination alone and chest radiography is of low utility in detecting asymptomatic recurrence (160). The Society of Gynecologic Oncology review further recommends that radiologic evaluation such as CT scan or PET/CT scan of the chest, abdomen, and pelvis should be used only to investigate suspicion of recurrent disease and not for routine surveillance after treatment (160). Several studies of patients with type I endometrial cancer and associated morbidity due to obesity, diabetes, and hypertension suggest that the long-term risk of death in these survivors often is associated with noncancer causes (162). After diagnosis of endometrial cancer, patients should be encouraged to make lifestyle changes, such as following a healthy diet and engaging in exercise, to reduce non-cancer-related risk factors (163, 164).
What is the role of estrogen therapy for the management of menopausal symptoms in survivors of endometrial cancer?

Of women undergoing hysterectomy and BSO for endometrial carcinoma, 25% are premenopausal. Many of these women will develop menopausal symptoms from the abrupt withdrawal of their ovarian-produced hormones. For these women, quality of life is extremely important and discussion of estrogen therapy is necessary. Traditionally, women with endometrial carcinoma have been denied estrogen because of the concern for increased risk of cancer recurrence. In patients with early-stage endometrial cancer, however, there is very little evidence to support a detrimental effect. The GOG undertook the only large, randomized, double-blind prospective trial of estrogen therapy versus placebo in 2,136 women with stage I and occult stage II endometrial cancer of all histologic subtypes who were enrolled within 20 weeks of undergoing hysterectomy and BSO (165). The study was closed prematurely when the Data Monitoring Committee determined that it would be impossible to accrue enough patients experiencing a recurrence in a reasonable amount of time to demonstrate a significant difference between the study groups. Outcomes were similar for those receiving estrogen therapy and those receiving placebo, including disease recurrence (2.3% versus 1.9%), development of a new malignancy (1.3% versus 1.6%), all-cause mortality (4.2% versus 3.1%), and death from endometrial cancer (0.8% versus 0.6%). Thus, estrogen therapy for the management of menopausal symptoms in the survivors of early-stage endometrial cancer can be considered after thorough counseling about the risks and benefits.

Summary of Recommendations and Conclusions

The following recommendations and conclusions are based on good and consistent scientific evidence (Level A):

- Outpatient endometrial sampling with disposable devices is reliable and accurate for the detection of disease in most cases of endometrial cancer and has become the method of choice for histologic evaluation of the endometrium.
- Hysteroscopy, although not required, is recommended with directed D&C to include any discrete lesions as well as the background endometrium.

The following recommendations and conclusions are based on limited or inconsistent scientific evidence (Level B):

- When transvaginal ultrasonography is performed for the initial evaluation of patients with postmenopausal bleeding and an endometrial thickness of less than or equal to 4 mm is found, endometrial sampling is not required.
- Endometrial thickness of greater than 4 mm in a patient with postmenopausal bleeding should trigger alternative evaluation (such as sonohysterography, office hysteroscopy, or endometrial biopsy), as should an inability to adequately visualize thickness.
- Because rare cases of endometrial carcinoma (particularly type II) can present with an endometrial...
Robotic-assisted laparoscopic staging is a feasible and safe alternative to traditional laparoscopy in women with endometrial cancer.

Lymphadenectomy may alter or eliminate the need for adjuvant therapy and its associated morbidity.

Optimal surgical cytoreduction (variably defined as less than or equal to 1 cm or 2 cm) has been found to improve progression-free and overall survival rates in patients with advanced-stage or recurrent endometrial cancer.

In women with gross residual disease, chemotherapy with paclitaxel and carboplatin is as effective as other regimens reported in the literature and has less toxicity.

The following recommendations and conclusions are based primarily on consensus and expert opinion (Level C):

Patients with low-grade disease (ie, grade 1 or grade 2 endometrioid lesions with less than 50% myometrial invasion and tumor size of 2 cm or less) seem to be at low risk of lymph node metastases and may not require a systematic lymphadenectomy.

Preoperative assessment of metastatic disease with imaging (computed tomography [CT], magnetic resonance imaging [MRI], or positron emission tomography [PET]/CT), measurement of serum CA 125, or both may be clinically important under special circumstances, such as when the patient is a poor surgical candidate because of medical comorbidities; when symptoms suggest possible metastasis to unusual sites, such as bones or the central nervous system; and when preoperative histology demonstrates a high-grade carcinoma (including grade 3 endometrioid, papillary serous, clear cell, and carcinosarcoma).

Vaginal hysterectomy may be an appropriate treatment for early-stage endometrioid endometrial cancer in select patients who are at high risk of surgical morbidity.

Chemotherapy and radiation therapy used in combination may offer superior outcomes compared with single-modality treatment.

In premenopausal women with endometrial cancer who want to retain ovarian function, ovarian conservation at the time of hysterectomy can be considered, but the decision should be individualized after evaluation of the risk of extrauterine disease and the potential for disease recurrence based on age, histologic cell type, and uterine tumor features.

Women found to have endometrial cancer incidentally after hysterectomy should have their risk of extrauterine disease and potential for disease recurrence evaluated based on age, histologic cell type, and uterine tumor features. Individualized treatment plans can be based on the findings.

Recommended surveillance after treatment of endometrial cancer includes a follow-up visit every 3–6 months for 2 years, then every 6 months for 3 years, and annually thereafter. Each follow-up visit should include a thorough patient history; elicitation and investigation of any new symptoms associated with recurrence, such as vaginal bleeding, pelvic pain, weight loss, or lethargy; and a thorough speculum, pelvic, and rectovaginal examination. Vaginal cytologic evaluation and annual chest radiograph are not recommended because most vaginal recurrences are detected with clinical examination alone and chest radiography is of low utility in detecting asymptomatic recurrence.

Radiologic evaluation such as CT scan or PET/CT scan of the chest, abdomen, and pelvis should be used only to investigate suspicion of recurrent disease and not for routine surveillance after treatment.

#### Proposed Performance Measure

Percentage of women with endometrial cancer undergoing minimally invasive comprehensive surgical staging

#### References


The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists’ own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 2000–November 2014. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

I  Evidence obtained from at least one properly designed randomized controlled trial.
II-1 Evidence obtained from well-designed controlled trials without randomization.
II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
III  Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.
Level B—Recommendations are based on limited or inconsistent scientific evidence.
Level C—Recommendations are based primarily on consensus and expert opinion.