



Review Article

Updates on Conservative Management of Endometrial Cancer

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ABSTRACT Endometrial cancer is the most common gynecologic cancer in the United States. It is typically diagnosed in postmenopausal women. However, given the increasing incidence of risk factors such as obesity and diabetes in younger women, it is becoming a more prevalent problem in this age group. When endometrial cancer is diagnosed in patients of reproductive age, the standard surgical option of hysterectomy and bilateral salpingo-oophorectomy may not be ideal for women interested in future fertility. Hence, conservative options for select patients should be discussed along with the associated outcomes of each approach. A number of studies have shown that in patients with complex atypical endometrial hyperplasia and grade I endometrial carcinoma, a conservative approach is safe and feasible. The aim of this review is to summarize published evidence of fertility-sparing options such as hormonal therapy, hysteroscopic resection of focal lesions, and the role of intrauterine devices. We will also provide the latest updates on ongoing prospective trials that explore strategies for conservative management in women with medical comorbidities or those interested in fertility preservation. *Journal of Minimally Invasive Gynecology* (2018) 25, 308–313 © 2017 AAGL. All rights reserved.

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Endometrial cancer is the most common gynecologic cancer in the United States with approximately 61 380 new cases expected in 2017, representing nearly 7% of all new cancer cases detected in women this year [1]. Although generally diagnosed in postmenopausal women, endometrial cancer is increasingly impacting younger women [2–4]. Approximately 7.1% of all women with endometrial cancer are diagnosed between the ages of 20 and 44 years [1]. Despite the fact that the incidence in this age group is low when compared with that in postmenopausal women, it is expected to continue to rise given the rising incidence of obesity and diabetes in this younger age group.

Among the most commonly identified risk factors in young women diagnosed with endometrial cancer is obesity because it is associated with peripheral estrogen conversion via

aromatization in adipose tissue [5]. A sedentary lifestyle is also considered a risk factor as evidenced by a recent meta-analysis that showed a 20% decrease in endometrial cancer risk in women who engage in high levels of physical activity [6]. As a composite, the aforementioned scenarios lead to hyperinsulinemia and type 2 diabetes, which are ultimately considered major contributors of cancer cell proliferation [7–9]. In addition, studies have shown that even among women who are genetically predisposed to endometrial cancer, as in the case of those with Lynch syndrome, the risk is significantly greater when they are concomitantly diagnosed with non-insulin-dependent diabetes and hypercholesterolemia [10]. Other potential risk factors, such as hypertension, nulliparity, early menarche, and anovulatory conditions, such as polycystic ovarian syndrome, also contribute to the development of endometrial cancer in young women [11].

A significant number of reproductive-age women are delaying childbearing, and this has led to an increasing number of nulliparous women at the time of their diagnosis; therefore, it is imperative to provide them with fertility-sparing options that will allow them the opportunity to get pregnant while at the same time provide them with adequate treatment of their cancer. In addition, it has been shown that endometrial cancer patients aged less than 45 years may have a more favorable prognosis than older patients. This is a result

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of a higher proportion of well-differentiated tumors and limited myometrial invasion in this younger age group [12–15]. To date, the overwhelming majority of options for conservative management of endometrial cancer center on treatment with oral progestins. Routinely, candidates for conservative management include those patients with a diagnosis of complex atypical endometrial hyperplasia or grade 1 endometrial carcinoma. More recently, other options have been presented including the use of a hysteroscopically guided resection of the endometrial cancer followed by hormonal therapy or the use of intrauterine devices (IUDs). It should be noted that the overwhelming majority of the literature on this subject is composed of retrospective series or review articles; thus, there is a paucity of data on prospective trials. The aim of this review is to summarize the current literature on conservative management of endometrial cancer with a focus on oncologic and obstetric outcomes.

Candidates for Conservative Management

The most recent National Comprehensive Cancer Network (NCCN) guidelines provide specific details regarding ideal candidates and options to be considered in young women interested in future fertility [16]. The patient must be diagnosed with well-differentiated (grade 1) endometrioid adenocarcinoma on dilation and curettage (D&C) that is confirmed by expert pathology review. Disease must be limited to the endometrium on magnetic resonance imaging (MRI) (preferred) or transvaginal ultrasound. There must be absence of suspicious or metastatic disease. There should be no contraindications to medical treatment or pregnancy. Currently, most clinicians agree that the only candidates for conservative management of endometrial cancer are women with anticipated stage IA (without myometrial invasion) grade 1 endometrioid cancer [17].

Diagnosis

An endometrial biopsy has been the hallmark study when diagnosing endometrial cancer. However, some have proposed that a pipelle biopsy may be inferior to a D&C when making this diagnosis. In a study by Leitao et al [18], the authors showed that by performing a D&C only 8.7% of patients were upgraded in the final specimen compared with 17.4% of those patients who had a pipelle biopsy ($p < .007$) [18]. One may also consider that a D&C may not only be diagnostic but also therapeutic because it may remove the tumor completely or partially, thus reducing tumor burden and facilitating the success of subsequent progestin therapy. The Society of Gynecologic Oncology recommends that the preferred tissue formats include curettage and biopsy and that devices that result in crushed, cauterized, or very small samples are unacceptable [19]. In addition, they recommend that exclusion of a concurrent carcinoma is necessary in all patients with a new diagnosis of atypical endometrial hyperplasia or endometrial intraepithelial neoplasia. One should also note

that establishing the histology of the tumor with certainty is of paramount importance because only endometrioid subtypes should be considered for conservative management. This highlights the need for review of the initial pathology by more than 1 pathologist or by a pathologist specializing in gynecologic cancers.

Role of Imaging Studies

Myometrial invasion is another important prognostic factor in patients with endometrial cancer. According to the Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) 26th Annual Report, the 5-year overall survival rate in patients with tumors limited to the endometrium is as high as 90.8%; however, this rate drops to 85.4% when deep myometrial invasion is identified [20]. The imaging study of choice for preoperative assessment of myometrial invasion is not specified; however, transvaginal ultrasound, computed tomographic imaging, and MRI are among the most frequently used [17]. Imaging is not only helpful to detect possible myometrial invasion but also to exclude synchronous ovarian tumors or suspicious lymphadenopathy. Based on the currently published literature, it seems that MRI is slightly more sensitive than ultrasound for the evaluation of myometrial invasion (86%–89% vs 66%–79%, respectively) [21,22] and that the implementation of both techniques reduces the false-negative and false-positive rates [23]. Kinkel et al [24] reported a significantly higher summary receiver operating characteristic value for contrast-enhanced MRI when compared with computed tomographic imaging and ultrasonography (0.91 vs 0.85 and 0.86, respectively; $p < .002$). Visualization with laparoscopy to evaluate for metastatic disease is not currently recommended. It is important to understand that, to date, there is no diagnostic tool that accurately predicts the grade or the depth of invasion of tumors without performing a hysterectomy.

Hormonal Therapy

When considering the pathophysiology of endometrial hyperplasia and cancer, it is well-known that endometrioid precancerous lesions arise from the prolonged exposure of the endometrium to estrogen without the opposing effect of progestins, which are associated with the inhibition of endometrial proliferation. Despite having shown efficacy, many studies have tested the presence of estrogen and progesterone receptors in an attempt to predict the response of treatment. However, recent guidelines are no longer routinely recommending this approach because it has been shown that even receptor-negative patients can respond to endocrine treatment [17].

The most commonly reported approach in the conservative management of patients with endometrial cancer is the use of progestational agents. The majority of patients reported in the literature have been treated with either medroxyprogesterone acetate or megestrol acetate. Unfortunately, there is no consensus on the optimal dosage and

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