International Journal of Women's Health

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REVIEW

Preserving fertility in young patients with endometrial cancer: current perspectives

This article was published in the following Dove Press journal:
International Journal of Women's Health
29 July 2014
Number of times this article has been viewed

Eleftheria Kalogera
Sean C Dowdy
Jamie N Bakkum-Gamez

Division of Gynecologic Surgery, Mayo Clinic, Rochester, MN, USA

Abstract: Endometrial cancer (EC) is the most common gynecologic malignancy in developed countries and affects predominantly postmenopausal women. It is estimated, however, that 15%–25% of women will be diagnosed before menopause. As more women choose to defer childbearing until later in life, the feasibility and safety of fertility-sparing EC management have been increasingly studied. Definitive treatment of total hysterectomy and bilateral salpingo-oophorectomy precludes future fertility and may thus be undesirable by women who wish to maintain their reproductive potential. However, the consideration of conservative management carries the oncologic risks of unstaged EC and the risk of missing a synchronous ovarian cancer. It is further complicated by the lack of consensus regarding the initial assessment, treatment, and surveillance. Conservative treatment with progestins has been shown to be a feasible and safe fertility-sparing approach for women with low grade, early stage EC with no myometrial invasion. The two most commonly adopted regimens are medroxyprogesterone acetate at 500–600 mg daily and megestrol acetate at 160 mg daily for a minimum of 6–9 months, with initial response rates commonly reported between 60% and 80% and recurrence rates between 25% and 40%. Photodynamic therapy and hysteroscopic EC excision have recently been reported as alternative approaches to progestin therapy alone. However, limited efficacy and safety data exist. Live birth rates after progestin therapy have typically been reported around 30%; however, when focusing only on those who do pursue fertility after successful treatment, the live birth rates were found to be higher than 60%. Assisted reproductive technology has been associated with a higher live birth rate compared with spontaneous conception, most likely reflecting the presence of infertility at baseline. Close follow-up is of paramount importance, and definitive treatment after completion of childbearing is advised.

Keywords: early stage endometrial cancer, fertility sparing, preserving fertility, conservative treatment, progestin, levonorgestrel intrauterine device

Introduction

Endometrial cancer (EC) is the most common gynecologic malignancy in developed countries, with an estimated 142,200 new cases in 2008 and an incidence rate of 12.9 per 100,000 women.[1] It is the third most common cause of gynecologic cancer death, with a mortality rate of 2.4 per 100,000.[1] In the US it is estimated that 52,630 women will be diagnosed with EC and 8,590 women will die from the disease in 2014.[2] Although the majority of women diagnosed with EC are postmenopausal, it is estimated that 15%–25% of women will be diagnosed before menopause;[2–8] 10% will be aged <45 years and 4% aged <40 years.[3,7]

The standard initial treatment for EC includes total hysterectomy and bilateral salpingo-oophorectomy (BSO) and/or pelvic and para-aortic lymph node assessment.[9]

Correspondence: Jamie N Bakkum-Gamez
Mayo Clinic, 200 First Street SW,
Rochester, Minnesota 55905, USA
Tel +1 507 538 5867
Fax +1 507 266 9300
Email bakkum.jamie@mayo.edu

Younger women tend to be diagnosed with low grade, early stage disease and have excellent prognosis with 5- and 10-year disease-free survival (DFS) of up to 99.2% and 98%, respectively.[10–13] Furthermore, prognosis tends to be more favorable in women aged <45 years compared with older women, whose 5-year DFS for low grade, early stage disease is only 86%.[7,10,11,13] Given the excellent oncologic outcomes associated with early stage EC in young women, the importance of improving quality of life and preserving fertility while maintaining excellent DFS has been recognized. This is especially important as an increasing number of women are choosing to defer childbearing until later in life. One out of 12 women is estimated to give birth after age 35 years today, compared with only one out of 100 in 1970.[14] As such, definitive surgical EC treatment may not be desired by women who have not completed childbearing. Fertility-sparing options for EC management have become increasingly investigated.

Several groups have described the feasibility and safety of fertility-sparing hormone therapy for early stage EC.[15–21] Despite the fact that hormone treatment of EC was first reported in 1961, a contemporary consensus standardizing conservative management does not exist. Specifically, there are various approaches to the initial assessment of young women with EC; the optimal agent, dosing, and duration of treatment are unclear; and surveillance modalities and frequency after treatment are not standardized. A novel hybrid approach that combines local hysteroscopic excision of the tumor with hormone treatment was recently introduced with encouraging results, yet only limited data are available, further complicating decision making.[22–24] Nonsurgical EC management is also challenged by the risk of missing an advanced stage EC, as well as the risk of missing an early stage synchronous ovarian cancer (OC). Additionally, the development of EC at a young age may be the herald of Lynch syndrome. Because the pathogenesis is less likely to be primarily related to a hormone imbalance, and hormone therapy may therefore be ineffective, identification of patients with Lynch syndrome is critical. Overall, counseling young women with an EC diagnosis on their options remains complex.

In this review we will present the current data and perspectives on fertility-preserving management of young women with EC. We will particularly focus on contemporary clinical trials and the controversies surrounding conservative management.

Hormone treatment

Progestin treatment

Patient selection

Although the majority of young women diagnosed with EC have early stage disease, there remains a non-negligible risk of disease extending beyond the uterus; the reported incidence of stage III or IV disease ranges from 10.5%[5] to 29.5%.[6,7] Additionally, there appears to be a higher rate of synchronous OC among young women with EC, ranging from 5% to 29%, compared with the overall risk of 5% of synchronous ovarian and endometrial malignancies among all women diagnosed with EC.[25–27] Specifically, Gitsch et al[6] observed a significantly higher incidence of synchronous ovarian malignancies in women aged <45 years with EC (29.4%) compared with their older counterparts (4.6%), and Walsh et al[25] reported that 25% of young women with EC in their cohort were found to have coexisting OCs. As such, proper patient selection for conservative EC management and thorough pretreatment evaluation are crucial.

Key parameters when assessing women for conservative management include grade of disease, depth of myometrial invasion, and the presence of adnexal masses. Although there is no consensus on the optimal workup, a thorough pretreatment evaluation for these parameters is necessary. Dilation and curettage (D&C) is recommended to best assess grade, as D&C appears to correlate better with final posthysterectomy grade compared with office endometrial sampling.[28] In addition, it has been suggested that D&C may offer a greater reduction of tumor burden compared with endometrial biopsy.[29]

Although various methods to evaluate myometrial involvement have been studied, including transvaginal ultrasonography and computed tomography (CT), contrast-enhanced magnetic resonance imaging (MRI) is most commonly utilized to estimate the depth of myometrial invasion. In a meta-analysis comparing the utility of CT, ultrasonography, and MRI, the range of sensitivity reported by different studies was 40–100% for CT, 50–100% for ultrasound, compared to 80–100% for contrast-enhanced MRI.[30] Sironi et al[31] evaluated the diagnostic performance of MRI in assessing the extent of myometrial involvement in patients with clinical stage I EC. The sensitivity of MRI to determine that the tumor was confined to the endometrium was 57%, with a specificity of 96%. Sensitivity and specificity were both 74% in determining the presence of superficial myometrial invasion (defined as presence of superficial myometrial <50% myometrial invasion). MRI carried a sensitivity of 88% and a specificity of 85% to determine deep myometrial invasion (defined as >50% myometrial invasion).[31] In a pooled analysis of prospective studies comparing T2-weighted and contrast-enhanced MRI, Wu et al[32] observed similar sensitivity (87% versus 81%, respectively), positive predictive value (64% versus 65%), and negative predictive value (84% versus 85%), whereas contrast-enhanced MRI had superior specificity

(58% versus 72%) when assessing myometrial invasion. Contrast-enhanced MRI may also provide information on lymph node status as well as cervical involvement in EC.[33] Furthermore, MRI is typically accepted as the next best imaging study following ultrasonography in characterizing an adnexal mass. In a meta-analysis focusing on the performance of different imaging modalities in diagnosing OC, estimated sensitivity was 86%–91% for ultrasonography, 91% for MRI, and 90% for CT. However, the diagnostic performance in detecting extrauterine disease spread in EC patients has been reported to be considerably lower; Zerbe et al[34] observed a 60% sensitivity of CT to detect adnexal involvement in EC patients. Given the apparent increased rate of synchronous ovarian malignancies among young women with EC and that pretreatment imaging and cancer antigen 125 are limited in their sensitivity to detect synchronous lesions, with up to 15% of EC patients with subsequently diagnosed adnexal involvement having normal preoperative imaging,[25] some gynecologic oncologists perform diagnostic laparoscopy at the time of initial evaluation.[35,36] However, even this approach is limited, as the presence of occult ovarian malignancy in the setting of intraoperatively benign-appearing ovaries has been reported to vary from 4% to 25%.[6,25,27,37]

Finally, pretreatment evaluation should include assessment for inherited gynecologic cancer syndromes such as Lynch syndrome. Additionally, it is important that women are counseled that a negative genetic evaluation does not exclude the risk of a synchronous or metachronous ovarian malignancy.

Ideal candidates for conservative management are young women with grade 1, early stage EC with no myometrial invasion who are highly motivated to maintain their reproductive potential and understand and are willing to accept the risks associated with deviation from the standard of care. Although this review will focus on this patient population, it is important to note that there are a few encouraging reports of conservative management of grade 1 EC with superficial myometrial involvement[38] and grade 2 or 3 EC with no myometrial invasion.[16,18,38–43] Given the paucity of data, conservatively managing higher grade disease should be considered with caution.

Agents, dosage, and duration of treatment

There is no consensus regarding the ideal progestin agent, dose, or duration of treatment. The two most common regimens are medroxyprogesterone acetate (MPA) at 500–600 mg daily and megestrol acetate (MA) at 160 mg daily.[44,45] In a recent systematic review and meta-analysis, Gunderson et al[46] reported that within the overall cohort, 49% received MPA, 25% MA, and 19% were treated with a levonorgestrel intrauterine device (LNG-IUD), though no comparison across types of progestin was performed. Evidence supporting the superiority of MPA over MA was recently published by Park et al,[45] who suggested that although response rates were similar between the two agents, MA was associated with a significantly higher risk of recurrence. Similarly, in a case series of grade 1 EC and complex atypical hyperplasia (CAH) previously published by our group, we observed a higher response rate to MPA compared with MA.[15] A wide range of MA and MPA doses has been reported, ranging from 10 mg to 400 mg daily for MA and from 2.5 mg to 800 mg daily for MPA.[44] Ushijima et al[47] observed better response with MPA at 600 mg compared with 200 mg or 400 mg daily, and other investigative groups have adopted this high-dose MPA regimen with similar outcomes.[18,48–53] However, similar to other published experiences,[21,49,50,54] all nine patients in our series treated with MPA received 10–20 mg daily and 88.9% had durable complete response, defined as complete initial response with no later recurrence.[15] Eftekhar et al[55] used an augmentation protocol that included use of MA at a starting dose of 160 mg daily for 3 months, with nonresponders receiving double the dose for an additional one or two 3-month periods, and observed complete response in 86% of the cohort with a mean treatment duration of 9 months. Although response rates to progestins are substantial, high doses of progestins also carry the risks of side effects and complications, with a higher likelihood of noncompliance. The choice of progestin, dose, and route of administration should be individualized to minimize risks such as thrombophlebitis, weight gain, headaches, sleep disorders, mood and libido changes, and leg cramps.[18,56,57]

An alternative to systemic progestins that may reduce these risks is the LNG-IUD. The LND-IUD has not been as well studied as oral progestins, but complete response rates from 40% to 100% have been reported in premenopausal women with well-differentiated, early stage EC.[58–60] None of these studies reported any specific difficulties with follow-up in the presence of an IUD, reflecting the fact that endometrial biopsy can still be performed with a Pipelle with the IUD in place.

When considering all progestin treatment options, the minimum duration of treatment needed to achieve disease regression appears to be 3 months.[20,56,61–63] However, the median duration of treatment required for disease regression appears to be 4–6 months.[15,20,21,47,51,53,64–68] Additionally, as obese and anovulatory patients tend to be more resistant to treatment, longer treatment durations should be considered among them.[16,45,69]

Surveillance for response to treatment

Close surveillance to evaluate treatment response is of paramount importance; however, a single standardized surveillance protocol does not exist. It is important to confirm disease regression from an oncologic standpoint as well as from a reproductive standpoint. Of note, there is not a universally accepted definition of complete disease regression, with some investigators considering the presence of simple hyperplasia and/or complex hyperplasia without atypia in follow-up biopsies as complete regression, while others do not. Although thinning of the endometrial lining on transvaginal ultrasound has been associated with favorable response to treatment,[47] documentation from tissue diagnosis, via either endometrial curettage or office endometrial biopsy, remains the standard criterion to assess response to treatment. Various intervals of follow-up have been reported, ranging from endometrial sampling every month[52,70] to every 6–7 months;[54,71–75] however, a 3-month interval appears to be the most frequent approach.[46] As 3 months of treatment appears to be the minimum required before disease response is observed,[20,56,61–63] a first follow-up sampling at 3 months would provide close surveillance while minimizing the frequency of an uncomfortable procedure between treatment initiation and expected response. However, individualization may be required for each patient, given the paucity of data and lack of consensus on surveillance interval.

The duration that each woman's cancer will remain in remission after progestin therapy cannot be predicted, and, as such, women achieving complete disease regression should be counseled to promptly pursue fertility if desired. Given that conditions such as polycystic ovarian syndrome are risk factors for both EC and infertility, it is also reasonable to consider early referral to a reproductive endocrinologist. Women not planning to attempt pregnancy immediately after achieving complete response should be placed on maintenance progestin therapy. Maintenance treatment with low-dose cyclic progestin or an LNG-IUD has been shown to lower the risk of recurrence after complete response among young women with EC undergoing fertility-sparing treatment.[45,47,62,76] Women with persistence or progression of their disease after 6–9 months of treatment[15,21] should be counseled about the lower likelihood of response with continuing treatment and the need to consider a more definitive approach.

Follow-up after successful treatment

Surveillance after successful response to treatment is essential, given the risk of EC recurrence as well as the risk of synchronous OC. Although recurrent EC tends to be confined to the uterus in the majority of fertility preservation cases, there have been reports of extrauterine spread, even in patients with complete response to initial treatment.[18,19,77] Follow-up surveillance should occur every 3–6 months after complete response and should, as a minimum, include a thorough pelvic examination, endometrial sampling, cancer antigen 125, and imaging, such as transvaginal ultrasound, MRI, and/or CT, to evaluate the adnexa.[45,54,62,66,78,79] As previously discussed, it is critical to underscore the importance of maintaining the patients on progestational therapy until pregnancy or hysterectomy, as well as between pregnancies.

Oncologic outcomes

The majority of young women with low grade, early stage EC who desire fertility preservation respond to progestin therapy. The range of response rates published in the literature varies, with some studies reporting response rates between 42% and 62%[48,54,60,68] and others reporting higher rates of 78%–100%.[52,62,65,66,76,80] Factors that could account for these differences include 1) variations in treatment duration, as longer treatment durations could result in higher response rates,[15,64] and 2) differences in definitions of "complete response". Some studies define complete response as no residual disease at follow-up endometrial biopsy, regardless of whether there is disease relapse in a future follow-up biopsy. Other investigators distinguish initial response from durable complete response.

In a meta-analysis of 32 studies published between 1985 and 2011, the estimated pooled disease regression rate (defined by the authors as lack of residual EC or CAH during follow-up endometrial sampling) was 76.2%, with median follow-up ranging from 11 months to 76 months.[44] In another review of 38 studies from 2004 to 2011, Gunderson et al[46] found an initial response rate of 74.6%, with 48.2% experiencing a durable complete response and 35.4% of the entire cohort experiencing a recurrence after initial complete response, with median follow-up from 2 months to 138 months. Additionally, 25.4% of the pooled cohort had persistent/progressive disease. These results are similar to the findings of Ramirez et al,[20] with an estimated initial response rate of 76% and an ultimate recurrence rate of 24% among initial responders, with median follow-up from 0 years to 30 years.

The duration of treatment required to obtain EC resolution ranges from 1 month to 17 months, and the most common estimated median time to response is 4–6 months.[15,20,21,47,51,53,64–68] Although lack of response

within 2 months of initiating progestin treatment has been suggested as a sign of lower likelihood of achieving complete response,[47] there is growing evidence that longer treatment with progestins (duration of treatment >6–12 months) is feasible and results in higher response rates without altering clinical/oncologic outcome.[15,51,64]

Although the rate of synchronous OC in women with EC aged ≤45 years has been reported to range from 5% to 29%,[25] in a recent meta-analysis the reported rate was only 3.6% among women opting for fertility-sparing treatment. As this meta-analysis included cases of CAH, the rate of 3.6% may be an underestimate of the risk among those diagnosed with EC.[44] Among reported cases of synchronous and metachronous OC, outcomes appear to be favorable, with long-term DFS and overall survival after OC diagnosis and treatment.[21,66] Nevertheless, a missed OC diagnosis or EC metastasis to the ovary in the setting of conservative EC management carries a risk of increased mortality. Thorough evaluation of the adnexae is critical, and, as noted, some surgeons advocate diagnostic laparoscopy prior to initiating progestin therapy to evaluate for extrauterine disease and primary ovarian malignancy.[35,36]

It is important to recognize that conservative treatment, although initially successful in the majority of women, is a temporizing measure. The risk of recurrence after completion of treatment is high, even among women who experience a rapid complete response, as well as among those on maintenance progestin therapy. EC recurrence rates range from 24% to 40.6%, and although most recurrences occur within the first 3 years of successful conservative therapy, recurrences can occur in as little as 2 months and up to 30 years after treatment.[20,44,45,64,81] Cumulative recurrence risk has been reported to be 51% after 3 years and 72% after 7 years.[64] Others have reported 5-year recurrence-free survival of 68%.[45] Nevertheless, most recurrences appear to be confined to the uterus. To date, there have been only seven patients reported in the literature with initial response to progestins who presented with advanced disease at the time of EC recurrence; however, four of them died of their disease.[18,47,53,77,82–84] And as the first EC-related death following successful fertility-preserving therapy was reported in January 2004, publication bias may be providing false reassurance.[65]

Standard treatment for recurrent disease after fertility-preserving treatment is hysterectomy, which precludes future fertility. As some women may still wish to maintain their reproductive potential despite recurrence, repeat fertility-sparing treatment may be considered. However, data supporting repeat progestin therapy in the setting of recurrent EC are even more limited than in the primary setting.[16,47,55,64,65,76,85,86] In 2013, Park et al[85] reported on the safety and efficacy of progestin retreatment in a cohort of 33 women with recurrent uterine-confined EC after initial successful progestin treatment. They observed a response rate of 85% after second-round progestin treatment, with a durable complete response rate of 85% over a median follow-up of 52 months. All but one patient were disease free at the end of the study (one patient was undergoing the third round of progestin treatment for multirecurrent disease). The few other published studies on outcomes of repeat fertility-sparing treatment have reported similar findings,[16,47,55,64,65,86] which suggests that progestin retreatment in the setting of initial complete response may be feasible and safe, albeit a temporary approach, for women who decline definitive treatment at the time of uterine-confined EC recurrence.

Among women who fail to achieve complete response and undergo definitive surgical management, most will have low grade EC on final pathology.[45,64] Recently, a cohort of 33 patients who failed progestin treatment and underwent hysterectomy was reported: 75.8% had grade 1 EC confined to the endometrium, 12.1% had atypical hyperplasia, and 12.1% had no residual disease.[45] However, progestin therapy does not preclude development of more aggressive histologies, and higher grade EC may be encountered at the time of hysterectomy.[5,53,58,76] It has also been reported that up to 13% of patients undergoing hysterectomy after failed progestin treatment will have higher grade disease.[58]

Few reliable predictors of disease treatment success have been identified.[45,50,87] Body mass index ≥25 kg/m^2 has been found to be associated not only with higher risk of progestin failure but also with higher risk of recurrence after complete response.[45] This finding underscores the importance of weight reduction in young EC patients desiring conservative management, as their disease is likely hormone dependent. Additional independent predictors of a lower risk of recurrence include successful subsequent pregnancy, use of maintenance progestin therapy, and use of MPA.[45] Molecular markers may also be able to predict response; the expression of phospho-Akt and phosphatase and tensin homologue within the primary prehormone-treated tumor appears to be associated with a higher risk of post-treatment hysterectomy among women opting for conservative progestin therapy for CAH and grade 1, stage IA EC.[50] However, these molecular markers are not currently clinically utilized.

Reproductive outcomes

In a recent review among 280 women conservatively treated for EC, 86 women achieved pregnancy (34.8%), with 89

total live births.[46] Another study reported a pooled live birth rate of 28%.[44] However, although all women included in these reviews reportedly wished to preserve their reproductive potential, not all attempted pregnancy during the respective study periods.[44,46]

Perhaps the most detailed pregnancy outcomes following progestin therapy were reported by Park et al[88] in 2013. Among 141 EC patients with complete response to progestin treatment, half attempted to conceive at a median time of 5 months after treatment completion. Pregnancy and live birth rates were 73% and 66%, respectively, for those who attempted pregnancy. However, when factoring in those who did not attempt pregnancy, the live birth rate was 26%,[88] which is similar to other reports.[44] Pregnancy rates between 40% and 50%,[42,52,68,76,79,89] or even higher,[49,64,90] have also been reported.

Although most providers would require complete regression of EC prior to encouraging pregnancy, one prospective study of conservative management of CAH and low grade, early stage EC allowed women to attempt pregnancy before achieving complete response, as pregnancy itself was considered to be a natural, extremely high-dose progestin therapy.[79] Although live births occurred in this study, there were also patients with persistent disease or EC relapse after pregnancy requiring definitive treatment. Of note, all patients were alive and free of disease at the end of the study, with a median follow-up of 98 months. Additionally, although the numbers are low, women who required more than 1 year to respond to progestins have had successful full-term pregnancies.[64] However, it is important to note that there are very few cases of successful pregnancy reported among women undergoing retreatment for EC recurrence after complete initial response.[64,76,85,88]

Cumulative data suggest that assisted reproductive technology (ART) is associated with a higher live birth rate compared with spontaneous conception in young women with EC. Lower spontaneous fertility rates could reflect the presence of EC risk factors that are also associated with infertility, such as obesity, polycystic ovarian syndrome, and chronic anovulation. In a recent systematic review, the live birth rate among women who underwent ART was significantly higher than the rate among the remaining women who were presumed to have attempted pregnancy spontaneously (39.4% versus 14.9%, respectively; P=0.001).[44] Also, although both EC and CAH cases were included in this analysis, the pooled live birth rate appeared to be comparable between the two groups (EC: 28% versus CAH: 26.3%). Better estimates of actual pregnancy success rates after ART compared with spontaneous pregnancy attempts are derived from studies including only women who do attempt pregnancy after progestins. In the Park et al[88] study, use of ART was associated with significantly higher pregnancy and live birth rates compared with women who attempted spontaneous conception (pregnancy rates: 86.4% versus 50%, P=0.001; live birth rates: 70.5% versus 42.3%, P=0.020). Similar promising outcomes supporting the use of ART in this patient population have also been reported.[49,58,62,64,76,89,90]

Following biopsy-proven complete disease regression, reproductive endocrinologists have used standard in vitro fertilization protocols for ovarian stimulation in the majority of the cases.[42,43,74,91–94] The safety of fertility drugs in this setting has been questioned, as the association between their use and the risk of EC is unclear.[95–98] In one study, the use of ART did not increase the risk of recurrence, nor did it influence the DFS.[88] Additionally, women who achieved pregnancy exhibited a better DFS compared with their counterparts, irrespective of fertility drug use. Collectively, there is growing evidence supporting the safety and feasibility of ART in young EC patients following successful fertility-sparing treatment.[64,68,99,100] In an effort to decrease the effects of estrogen exposure to the endometrium, Juretzka et al[101] used a PG-IUD during ovarian stimulation. Toward this direction, Azim and Oktay[102] suggested in 2007 an ovarian stimulation protocol based on the use of letrozole, an aromatase inhibitor, in conjunction with gonadotropins, which was associated with lower estrogen levels compared with standard stimulation cycles as well as good reproductive outcomes. The authors suggested the use of letrozole not only on the basis of its ovulation induction effect and their prior experience with a similar ovulation induction protocol in breast cancer patients but also for its relative safety in EC patients.[103–106]

In summary, early referral to reproductive endocrinology in the setting of fertility-sparing EC treatment should be considered in order to maximize the likelihood of a live birth and minimize the time between diagnosis and definitive EC treatment.

Definitive treatment

Women failing conservative treatment due to either disease progression or lack of regression should undergo definitive treatment consisting of hysterectomy, BSO, and/or lymphadenectomy. Definitive surgery should be considered if no evidence of disease regression is observed within 6–9 months of treatment initiation, as the likelihood of success with further treatment is low. Even if conservative treatment is initially successful with biopsy-proven regres-

sion of disease, 40.6% of responders will recur, even despite the use of maintenance therapy.[44,45] Therefore, once women who have been successfully treated with progestins have completed childbearing, they should undergo definitive surgery. Also, given the limited data on the safety of progestin retreatment in the setting of recurrent disease,[16,47,55,64,65,76,85,86] those who experience recurrence should also undergo hysterectomy, BSO, and/or lymphadenectomy. Women who decline definitive treatment after appropriate counseling should be carefully followed.

Ovarian preservation in the setting of surgical treatment

The risks and benefits of ovarian preservation in young women with low grade, early stage EC undergoing definitive treatment require individualization.[107–110] The safety of ovarian preservation in young women with EC has been studied via the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database.[108] Among 3,269 women aged ≤45 years, 12% had ovarian preservation. In a multivariate Cox model, ovarian preservation had no effect on cancer-specific or overall survival. Additionally, in a retrospective cohort of women aged ≤45 years representing all stages of EC, although BSO appeared to lead to better DFS, especially in stage I disease, it did not appear to improve overall survival.[110] Similarly, in 2013, Sun et al[109] found that ovarian preservation did not negatively impact overall survival in a cohort of 166 young Chinese women with EC. Nonetheless, it is important to recognize that ovarian preservation carries a potentially life-threatening risk of missing occult synchronous ovarian malignancy or metastatic disease,[5,6,25,107,111] even if the ovaries appear benign during intraoperative inspection; in fact, among all synchronous cases of EC and OC, approximately 15% may have macroscopically normal-appearing ovaries at the time of surgery.[25]

Ovarian preservation does, however, afford an opportunity for fertility preservation in the setting of hysterectomy, given the potential for future oocyte retrieval and surrogacy, both of which are emerging concepts in the fertility preservation literature.[112–114]

Nonhormone conservative treatment

Photodynamic therapy (PDT) has recently been introduced as a novel treatment modality for early stage EC[115] and has previously been reported as treatment for esophageal, endobronchial, bladder, vulvar, vaginal, and cervical cancers and precancerous lesions.[116–123] PDT uses a nontoxic light-sensitive compound (photosensitizing agent), which upon selective exposure to light of a specific wavelength produces active oxygen species that are toxic to surrounding cancer cells.[124] The selection of the specific photosensitizing agent and corresponding wavelength depends on the distance that the light needs to travel in order to target the cancer. In 2013, Choi et al[115] published the outcomes of a cohort of 16 young EC patients pursuing fertility-sparing management who were treated with PDT. Among them, PDT was used as the primary treatment in eleven patients and as secondary treatment for recurrence after failed hormone therapy in five patients. The initial response rate was 75% (12/16) and recurrence rate was 33% (four/12). Of the four patients who recurred, two elected to undergo definitive surgical treatment and two continued PDT with complete response (one patient after one additional PDT course and one after two courses). The pregnancy rate was 57%. The only adverse effect that was observed was mild facial angioedema in 25% of the patients, which was managed conservatively. Recognizing that this is a single report, the authors concluded that PDT could potentially be an effective conservative treatment method for highly motivated women who wish to pursue fertility-sparing treatment.[115]

Fertility-sparing surgical treatment

A few investigators have suggested hysteroscopic surgical excision of the lesion followed by progestin as an alternative conservative management approach in young women with EC.[22–24] In 2009, Mazzon et al[24] published a case series of six patients with stage IA EC who underwent conservative resectoscopic treatment using a three-step technique first reported in 2005. First, the tumor was removed; second, the endometrium adjacent to the tumor was removed; and, third, the myometrium underlying the tumor was resected.[23] If final pathology confirmed grade 1 EC with no myometrial invasion, patients were subsequently treated with progestins for 6 months. There were no complications related to the hysteroscopic surgery, and all women had complete regression of disease after 3 months' treatment. Importantly, there were no recurrences after a median follow-up of 50.5 months. Four out of the six patients had successful pregnancies without the use of ART, at a median time of 24 months after treatment completion, and two were actively attempting pregnancy when the study was published.[23] In 2011, Laurelli et al[22] published a study of 14 stage IA EC patients using a similar approach of combined operative hysteroscopy and hormone therapy. Similar to Mazzon et al,[24] no perioperative complications were observed, and all patients had initial response to treatment.

Only one woman experienced disease recurrence 5 months after hysteroscopic resection, and she was subsequently managed with hysterectomy. At a median follow-up of 40 months, all patients were alive with no evidence of disease. Of the three patients who attempted to conceive, ART was not utilized and there was one live birth. Although these preliminary reports are promising, larger studies are necessary to further assess safety and efficacy of combined hysteroscopic resection and progestin therapy as an option for fertility-preserving management of young women with EC.

Conclusion

Although fertility-sparing management of EC is not the current standard of care for young women with EC, it may be considered for those patients with low grade, apparent early stage disease who wish to maintain their reproductive potential. Candidates should be carefully selected using strict selection criteria (grade 1, early stage EC with no myometrial invasion; highly motivated to maintain their reproductive potential; fully comprehend and are willing to accept the risks associated with deviation from the standard of care; and agreeable to a close follow-up schedule) and thoroughly counseled on the oncologic risks associated with unstaged EC as well as the risk of synchronous OC. Pretreatment assessment of the extent of disease to rule out myometrial invasion and/or extrauterine spread is essential, with MRI currently being the most sensitive imaging modality to detect myometrial invasion while having a diagnostic ability to detect adnexal involvement comparable with transvaginal ultrasonography. Although the ideal treatment regimen is yet to be determined, recent data suggest that MA may be associated with a higher risk of recurrence compared with MPA. The LNG-IUD is increasingly emerging as an alternative to oral progestins; however, more prospective studies with longer follow-up periods are warranted before definitive conclusions can be drawn on its efficacy and safety in the conservative treatment of EC. The majority of patients will respond after 4–6 months of progestin treatment. However, time to complete resolution of EC can vary from as soon as 3 months to more than 1 year, with data suggesting that a trial of 1 year of treatment with close follow-up is reasonable before abandoning progestins. Ultimately, a considerable subset of those experiencing complete response who will attempt to become pregnant will have live births. It is also important that patients are counseled early about the higher live birth rates associated with ART and the potential need for this technology. Despite highly durable complete response rates of 50%–75%, the risk of recurrence remains a reality even for those with complete initial response. Close follow-up is essential, and definitive treatment after completion of childbearing is recommended. The risk of localized EC recurrence should not discourage physicians from offering fertility preservation options to highly motivated women. Alternative approaches to progestins alone include PDT and hysteroscopic EC excision followed by progestin treatment, and these have had encouraging results; however, larger studies are needed as the current data are limited. The majority of data to date are from retrospective observational studies. However, large prospective trials on conservative management of early stage EC and/or CAH with progestins, LNG-IUD, or a combination of both, are emerging (http://www.clinicaltrials.gov: NCT00788671, NCT01074892, NCT00483327, and NCT01594879). Further assessment of oncologic and reproductive outcomes through high-quality prospective clinical trials will help guide standardization of treatment, surveillance, and overall management of young women with EC who desire fertility preservation.

Disclosure

The authors report no conflicts of interest in this report.

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