Current Clinical Oncology
DOI 10.1007/7631_2015_2

Primary Hormonal Therapy of Endometrial Cancer

Linda R. Duska

Abstract

This chapter discusses the treatment of endometrioid adenocarcinoma of the endometrium in premenopausal women with hormonal therapy for the purpose of preserving the corpus and future fertility. In addition, postmenopausal women who are not candidates for surgery may benefit from similar approaches.

Keywords

Endometrial cancer • Premenopausal • Fertility preservation • Hormonal treatment

Introduction

Endometrial cancer is the most common of the gynecologic malignancies. In 2014, 52,630 cases of endometrial cancer and 8,590 deaths from the disease are estimated in the USA [1]. Most endometrial cancers occur in women who are postmenopausal, and therefore completed their childbearing. However, a small percentage of endometrial carcinomas occur in women who perhaps have not yet begun or not completed their families.

L.R. Duska (✉)
Professor of Obstetrics and Gynecology, Department of Gynecology Oncology, University of Virginia Medical Centre, PO Box 800712, Charlottesville, VA 22908, USA
e-mail: lrd5d@hscmail.mcc.virginia.edu

The standard of care for endometrial cancer is surgery. The primary surgery consists of total hysterectomy with the removal of both tubes and ovaries. In the USA, this is often associated with staging surgery, including removal of the pelvic and para-aortic lymph nodes [2]. The surgery may be performed via laparotomy or more commonly via a minimally invasive approach. Obviously, this surgical treatment will make future childbearing for the patient impossible. With surgical staging and adjuvant therapy where appropriate, the 5-year survival for endometrioid endometrial cancer confined to the corpus is 95 %. For those women who have non-myoinvasive grade 1 disease, the disease free 5-year survival following surgical therapy is 99.2 % [3].

This chapter discusses alternative treatment of endometrioid adenocarcinoma of the endometrium

with hormonal therapy for the purpose of preserving the uterus and therefore future fertility. Mainly retrospective data will be discussed, although recent prospective studies also exist and will be presented. It should be stressed, however, that the treatment of endometrial cancer with less than hysterectomy at the current time represents a therapy that is outside of the "standard of care," and therefore should be undertaken with caution with a well-informed patient and an experienced physician.

This discussion will also apply to older women with endometrial cancer who are not surgical candidates for medical reasons. Limited data are now available in this population, though hormonal treatment has a higher rate of success in the premenopausal population. However, many of these older women for whom fertility is not an issue may be better served by primary radiation therapy if they cannot undergo surgery.

Epidemiology

Endometrial cancer most often affects postmenopausal women, with over 70 % of cases occurring in the postmenopause and a mean age of diagnosis of 62 years [4]. Endometrial cancer is most frequently diagnosed in women ages 55–64 years, with the majority of cases diagnosed in women ages 45–74 [4]. However, retrospective reports suggest that between 2 and 14 % of women presenting with endometrial cancer will be less than 40 years old [5–14]. This premenopausal group has both similar and different epidemiologic characteristics than the postmenopausal age group that need to be considered. Moreover, because of their young age, the diagnosis of endometrial cancer is not always entertained in these patients when they present with menstrual irregularities.

Fortunately, premenopausal women with endometrial cancer have a higher rate of low-grade tumors as well as a higher rate of low-stage disease when compared to older patients, resulting in a favorable disease-specific survival rate [15]. One of the largest single institution studies of women under the age of 45 years with endometrial cancer was reported from Yale [16]. A total of 251 patients were identified, 75 % of whom had stage I disease. The majority of patients had grade 1 disease (53 %) with only 5 % having high-grade tumors. Eighty-seven percent of patients had endometrioid histology.

One of the epidemiologic risk factors shared by women of all ages with endometrial cancer is obesity. With the rise in obesity in the USA and the world, the number of endometrial cancer cases is also expected to increase [17]. As a woman's weight increases, so to does her risk for endometrial cancer [18]. Obese women are two to three times more likely to get endometrial cancer than their lean counterparts [19, 20], and women who are 50 pounds overweight are ten times more likely to develop endometrial cancer [21].

Several large retrospective studies have considered obesity rates specifically in younger women with endometrial cancer (defined in most series as a BMI >30). The largest studies that have data regarding BMI in this younger age group are shown in Table 1. If all studies, including those that measure obesity by body weight alone, are included, obesity rates in younger women range from as low as 29 % to as high as 73 % [14]. Interestingly, the obesity rates in young women seem to be higher than those of older women within the same population. For example, in the series from Gallup et al., an obesity rate of 43.8 % in women <40 years

Table 1 Obesity data for women with endometrial cancer ages 40 [47] and under

	Duska [14]	Gitsch[a] [11]	Soliman [13]	Walsh[a] [22]	Park[b] [23]	Wang [24]	Totals
#	92	17	79	102	48	37	375
BMI ≥30	44	6	48	46	23	11	178
Obese (%)	48	35	62	48	48	32	48

[a]Included women up to age 45 years
[b]Data is for BMI ≥25

with endometrial cancer contrasted with 18 % in a group of patients treated at the same institution who were over 40 years of age [8]. Reported obesity rates in young endometrial cancer patients are lower in the series reported from Asian countries.

All young women with endometrial cancer are not obese; in fact, many of them will present with normal weight. In the series from Massachusetts General Hospital (MGH), 52 % of women <40 years with endometrial cancer were of normal weight (BMI < 30), and 43 % had a BMI of 25 or less [14]. In that study, there was a trend toward higher stage disease and high-risk histology in the normal weight women, though the differences did not reach statistical significance. Schmeler et al. presented a series of women <50 years and of normal weight seen at the MD Anderson Cancer Center [22]. They suggested that hormonal factors, and in particular polycystic ovarian syndrome (PCOS), might be a risk factor for developing endometrial cancer in these women with normal weight. Retrospective data suggests that normal weight younger women are not at higher risk for poor survival, though the numbers are too small in all studies to reach any conclusion.

Obviously, women <40 do not present with postmenopausal bleeding or staining. However, the majority of young women with endometrial cancer will present with some type of menstrual irregularity. In the series from MGH, 29 of 91 (32 %) women presented with menorrhagia or increasing menorrhagia and 39 of 91 (43 %) presented with irregular menses or menometrorrhagia [14]. Similarly, 26 of 32 (81 %) women in the Crissman series and 77 % of the patients in the Yale series presented with irregular vaginal bleeding [7, 16]. Other studies have also reported high rates of irregular bleeding as the presenting complaint [6, 9, 12]. Persistent irregular bleeding, therefore, merits endometrial sampling even in those women age <40 to rule out an underlying endometrial neoplasm.

Infertility is also a hallmark of women <40 with endometrial cancer, in contrast to their postmenopausal counterparts, who are often characterized as "fertile." In the MGH series, 11 patients (12 %) were diagnosed with endometrial cancer incidentally during infertility evaluation [14]. In Gallup's study, 44 % of women <40 years with endometrial cancer were classified as "infertile," though information is not provided to suggest that infertility was the presenting symptom prompting evaluation [8]. Schmeler's study reported a 17 % risk of infertility in women under age 50 with endometrial cancer [22]. A large study from Korea reported an infertility rate of 38.3 %, which was higher than that of their general population (10–15 %) [23]. It is likely that in many of these cases, the infertility is a result of anovulation, associated with high levels of circulating unopposed estrogen. In a study from Taiwan, for example, 13 % of patients met the criteria for polycystic ovarian syndrome [24]. Unfortunately, all data is retrospective and often limits obtaining hormonal information about patients unless it is specifically documented in the patient's chart.

Genetic disorders, particularly hereditary nonpolyposis colon cancer or Lynch syndrome, are associated with endometrial cancer, usually at a young age. In fact, endometrial cancer is the most common cancer of Lynch syndrome in women and may be the presenting cancer in some patients [25]. A detailed family history is instrumental in making this diagnosis, and all young women presenting with endometrial cancer should have a careful family history taken.

Finally, endometrial cancer in a young woman may result from an estrogen-producing ovarian tumor, such as a granulosa cell tumor. Clinically, a very young woman may present with an ovarian mass, irregular bleeding, and/or infertility. Treatment of the ovarian tumor must include dilatation and curettage (D&C) to rule out an underlying endometrial neoplasia.

Complex Atypical Hyperplasia in Women Under 40 Years

The issue of complex atypical hyperplasia (CAH) needs to be addressed, particularly in the setting of a discussion of treating young women with grade 1 endometrial cancer with hormones rather than definitive surgery. While CAH is a

precancerous lesion, it cannot reliably be stated that there will be no cancer on the hysterectomy specimen when a preoperative diagnosis of CAH is made. The possibility of an underlying grade 1 (or higher) endometrioid adenocarcinoma must be considered when treating CAH with hormones for the purpose of preserving fertility.

Kurman et al. established retrospectively that a preoperative diagnosis of CAH resulted in a postoperative diagnosis of grade 1 adenocarcinoma on the hysterectomy specimen in 29 % of cases [26]. This study has since been repeated prospectively by the Gynecology Oncology Group (GOG) [27, 28]. The GOG study entered women with a preoperative "community" diagnosis of CAH, all of whom underwent hysterectomy within 12 weeks of diagnosis. All preoperative specimens were reviewed by a panel of "expert" pathologists, as were the final hysterectomy specimens. The rate of carcinoma in the final hysterectomy was 43 %, much higher than in Kurman's retrospective study. In addition, the community diagnosis of CAH was supported by the expert panel in only 38 % of cases. In 29 % of cases, the expert panel felt that the lesion merited a diagnosis of carcinoma. Finally, there was complete agreement of the experts in only 40 % of cases.

From the data presented above, it is clear that CAH on an endometrial biopsy needs to be treated as if an endometrial cancer might be present in the uterus. Care should be taken to exclude carcinoma as a possibility, either via D&C as the "gold standard," slide review by an expert pathologist, or both when considering treatment with hormones and conservation of the uterus.

Staging

Endometrial cancer has been surgically staged since 1988, with the publication of the results of the surgical staging study GOG 33 [29]. This study demonstrated the importance of lymph node status as well as depth of myometrial invasion as markers of prognosis and recommendations for adjuvant therapy. After that publication, for years the GOG defined surgical staging of endometrial cancer as including: exploratory laparotomy, pelvic washings, total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), and sampling of pelvic and para-aortic lymph nodes. Over the past decades, however, the GOG and others have published data to suggest that minimally invasive surgery is an appropriate method for surgical staging [30]. In addition, updates to International Federation of Gynecology and Obstetrics (FIGO staging) have removed pelvic washings as part of the staging criteria [2].

The criteria defined by GOG 33 also helped clinicians to predict which patients might have positive retroperitoneal lymph nodes based on the grade of disease and depth of myometrial invasion, and by extension which women would benefit from retroperitoneal node dissection [29]. In GOG 33, women with grade 1 tumors and no myometrial invasion had a 0 % rate of positive pelvic or para-aortic retroperitoneal lymph nodes. In fact, the rate of lymph node metastases for noninvasive carcinoma of any grade was less than 3 %. However, deeply invasive grade 1 tumors had an 11 % rate of positive pelvic lymph nodes and a 6 % rate of positive para-aortic lymph nodes, indicating the need for adjuvant therapy after surgery and a poorer prognosis. Therefore, a patient with a grade 1 carcinoma that is (clinically) noninvasive has a theoretical risk of positive retroperitoneal nodes of 0 %, making her an ideal candidate for hormonal therapy.

When a clinician is considering managing a patient with hormonal treatment, however, surgical staging is not possible. The determination of clinical staging, then, must be made with the best available data, the limitations of which will be discussed below, with surgical staging considered to be the "gold standard." Since it is generally accepted that only patients with noninvasive endometrial cancer (and grade 1 or at most grade 2 endometrioid histology) should be managed with hormones, the clinician needs to use all possible modalities to assure that the patient has "clinical" non myoinvasive grade 1 disease. For the purposes of the remainder of this discussion, it will be assumed that all histology is endometrioid since hormonal management of

any other histology of endometrial cancer is not appropriate.

Grade

Preoperative tumor grade is not always predictive of tumor grade on the final hysterectomy specimen. Cowles et al. demonstrated that preoperative grade 1 tumors were upgraded at the time of hysterectomy in 11 % of cases [31], while a larger study by Daniel et al. reported an overall upgrading of 15–20 % [32]. In combination, the two studies did demonstrate that we do best predicting postoperative grade correctly when the preoperative grade is 1. Eltabbakh et al. reviewed 182 patients at their institution who underwent surgical staging for preoperative grade 1 tumors [33]. In 30 % of cases, the grade was changed on the hysterectomy specimen. In 22 % and 6 % of cases, the postoperative grade was 2 and 3, respectively. Obviously, then, there is a not insignificant risk that a young woman presenting with a grade 1 tumor will have a higher grade histology discovered if she undergoes hysterectomy, and therefore increased risk of disease outside of the uterus. Since D&C is considered the "gold standard" for preoperative diagnosis, hormonal management of a young patient should always be preceded by a D&C rather than an endometrial biopsy only.

Myometrial Invasion

There is no 100 % reliable method to determine the depth of muscle invasion short of removing the uterus and examining the myometrium microscopically. Most clinicians will use a combination of MRI, ultrasound, and/or CT scanning to make the diagnosis of clinical stage I non-myoinvasive disease. None of these modalities are completely reliable, and all are more accurate when diagnosing deep rather than superficial myometrial invasion.

CT scan is useful for identifying large volume extrauterine disease, but fails to detect microscopic lymph node metastases. Accuracy of CT scan in predicting myometrial invasion ranges from 61 to 76 %, increasing to 83 % with deep invasion [34–36]. Zerbe et al. reviewed their experience with preoperative CT scans in predicting the extent of myometrial invasion [37]. All patients had a CT scan performed within 10 days of surgery and the results were classified as $>$ or $<$50 % invasion. In this study, CT scan failed to identify 17 of 44 patients (39 %) who had myometrial invasion. While this study did not look specifically at grade 1 tumors, it suggests that CT is not useful in determining myometrial invasion. Other authors have confirmed this finding [38].

MRI can be useful for evaluating myometrial invasion as well as pelvic nodes and adnexal masses. Many studies about the MRI accuracy in myometrial invasion detection have been published, and the accuracies showed a wide range of variation (66–95 %) with limited number of patients included [39–47]. The accuracy of T2-weighted images in the determination of myometrial invasion by endometrial carcinoma varies between 68 and 82 % [42, 43, 48]. The use of a dynamic study after administration of intravenous contrast increases the accuracy of myometrial invasion to 85–91 %, respectively [43, 49, 50].

In the paper from Sanjuan et al. [51], 72 consecutive patients with endometrial cancer underwent preoperative MRI, and MRI results were compared to final histopathologic findings. Sensitivity, specificity and accuracy of MRI for the detection of myometrial invasion $\geq$50 % were 71 %, 86 %, and 58 %, respectively. This study used both T2 and dynamic images, and only 10 patients in this series had noninvasive endometrial cancer.

Suh et al. reported a retrospective review of 301 patients, all of whom underwent preoperative MRI and had stage I disease on MRI [47]. On final pathology, 17 patients had higher stage disease. Of the remaining 284, 124 had no invasion on preoperative MRI, but only 61 of these women had no myoinvasion on final pathology of the uterus. The negative predictive value of absence of myometrial invasion was 49.2 %. MRI showed an accuracy of 59.2 %, a sensitivity of 68.8 %, a specificity of 74.4 %, and an 86.9 %

positive predictive value for myometrial invasion. Another study showed a similarly low negative predictive value for myoinvasion of 42.2 % [41]. Even when dynamic study was applied, the value improved up to 60 %. Despite the low negative predictive value for myoinvasion, MRI can correctly differentiate whether or not there is deep myometrial invasion [52–55].

Of note, there may also be significant consequences to a false positive MRI result. For example, Ohio State reported a case of a 29-year-old G0 with grade 1 endometrial cancer who wanted to preserve fertility [56]. As part of the evaluation, an MRI suggested myometrial invasion and for this reason a TAHBSO was performed. The final pathology revealed only decidualized endometrium consistent with progesterone use. This case represents a case of a false positive MRI with resulting loss of fertility.

It must also be noted that for both CT and MRI, the postmenopausal woman presents a special diagnostic challenge because of the lack of junctional zone between the endo- and myometrium. It is likely that accuracy will be higher in premenopausal women. Tumor grade, however, did not seem to be a factor in predicting myometrial invasion in one meta-analysis [57].

Despite the above noted limitations, MRI is the most frequently recommended modality for assessing myometrial invasion in the premenopausal woman wishing to preserve her uterus. Contrast-enhanced MRI improves accuracy [50, 53]. Transvaginal ultrasound can also be utilized to exclude ovarian lesions. Like CT, MRI will not be able to accurately diagnose microscopically positive retroperitoneal lymph nodes.

Data Supporting Hormonal Therapy

Retrospective

The majority of historical data supporting hormonal therapy of endometrial cancer is retrospective and, therefore, subject to reporting bias. Most older series are small, with numbers of patients reported ranging from 1 to 15. Recent studies include both complex atypical hyperplasia (CAH) and grade 1 endometrial cancer and have more patients, but the numbers are still low, with 19 CAH and 25 endometrial cancer in one study [58], and 37 patients with only endometrial cancer in another [24].

Ramirez et al. published a literature review of retrospective patients treated with progesterone [59]. They identified 27 studies describing 81 patients treated with hormones for endometrial cancer. Overall, the response to progestin therapy was 76 %, with a median time of response of 12 weeks. Documentation regarding pregnancy was available for 20 patients, all of whom were able to conceive at least once following treatment. Gottlieb et al. performed a similar and more comprehensive literature review and identified 101 women with a mean age of 29 years treated with hormones for endometrial cancer, with a 71 % initial response rate, minimal time to response of 3.6 months, and 56 live births [60]. Most recently, two meta-analyses of oncologic and fertility outcomes with both atypical hyperplasia and grade 1 adenocarcinoma have been reported: both revealed an overall approximate 80 % response to treatment [61, 62].

Historical Retrospective Studies of Interest

One of the earliest and largest retrospective studies was that of Bokhman et al., in 1985 [63]. It preceded surgical staging, and all patients at that time were clinically staged. Nineteen patients ranging in age from 19 to 37 (mean 28.7) years with endometrial cancer were treated with progesterone, 11 patients with grade 1 tumors, and 8 with grade 2 tumors, all with clinical stage I disease. Seventeen patients had primary infertility and 14 were obese. All patients were treated with 500 mg daily of IM oxyprogesterone caproate. All patients who did not demonstrate response after 3 months underwent hysterectomy. In total, 15 of the 19 patients were cured with hormonal therapy. Data regarding live births following treatment was not reported.

The next consecutive larger series was reported by Randall and Kurman in 1997 [64].

While this study is often quoted, it consisted of a retrospective review of cases sent to Johns Hopkins Hospital for pathology consultation rather than as a report of women treated at a single institution. Fourteen women were treated with hormones for grade 1 adenocarcinoma. Most of the patients were described as treated with "high-dose progestins," though the treatments were not standardized as they were in the previous report. In this study, no woman had tumor progression defined as an increase in grade on subsequent sampling. Two women were found to have coexisting ovarian carcinomas following hormonal therapy and underwent surgery; in both cases, a stage IA grade 1 endometrioid adenocarcinoma was confirmed histologically. Three women had five full-term deliveries. One patient experienced recurrence of her cancer after initial response to therapy. She had another complete regression after reinstitution of progesterone therapy, and ultimately had a full-term delivery.

In 2001, the group from MGH presented a retrospective review of 12 patients who underwent hormone therapy of endometrial cancer [14]. The patients ranged in age from 24 to 40 years and 8 presented with infertility. All patients had grade 1 tumors. Two patients eventually underwent hysterectomy for persistent disease, and one of these developed a synchronous ovarian primary tumor. Four women achieved pregnancy with five viable infants delivered.

Gottlieb et al. in 2003 reported 13 patients with ages ranging from 23 to 40 (mean 31) years [60]. In six patients, the diagnosis was made during infertility evaluation. Eleven patients had a grade 1 tumor and two had a grade 2 tumor. All patients received treatment for at least 3 months and all responded to therapy with regression of their disease documented by endometrial biopsy. Progestin therapy was not standardized; eight patients were treated with megestrol acetate 160 mg daily. Five patients developed local recurrence. Three patients delivered nine viable infants and two further patients were pregnant at the time of the report.

Larger Retrospective Studies from Combined Centers

More recently, several groups have reported larger series of women with both CAH and endometrial cancer treated with progesterone therapy. The Korean group searched eight tertiary cancer centers to collect 148 women less than or equal to 40 years old who were treated with progestin for stage IA grade 1 endometrioid adenocarcinoma of the endometrium [65]. In this series, 115 patients (78 %) showed a complete response to progestin, with a mean duration of treatment of 8 months (range, 2–31 months). All patients were treated with either oral medroxyprogesterone acetate or megestrol acetate continuously. Body mass index greater than or equal to 25 kg/m^2 was the only significant factor associated with a failure to achieve CR. Thirty-five patients (30.4 %) experienced disease recurrence. The use of medroxyprogesterone acetate was associated with a higher risk of recurrence than the use of megestrol acetate. The possible superiority of megestrol acetate was also confirmed by a meta-analysis from France [62]. The same Korean group also reported a retrospective cohort study of 48 women age 40 and under who were treated conservatively, with similar results [66].

The group from Toronto reported a series of 44 women, 19 with CAH and 25 with grade 1 endometrial cancer [58]. Twenty-four patients achieved a complete response (CR) to progesterone treatment, with a median time to CR of 5.7 months. Ninety-two percent of patients had responded within 12 months. Older age at diagnosis was associated with a lower likelihood of complete response, as was higher BMI. Thirteen patients (54 %) who achieved a CR experienced disease recurrence.

The group from Taiwan reported 37 patients with grade 1 endometrial cancer treated between 1991 and 2010. In this study, the mean follow-up was lengthy (78 months). Complete response lasting more than 6 months was achieved in 81 % of patients, and like the study from Toronto, responders were significantly younger

than nonresponders. Older women were also more likely to experience disease recurrence.

Finally, one small but provocative study tried to identify predictors for response to or failure of progesterone therapy [67]. The study made the following four important observations: (1) there was a negative correlation between extent of pretreatment architectural abnormality and disease resolution; (2) for patients without significant architectural abnormality, resolution was associated with BMI, with a BMI < 35 associated with the highest resolution rate; (3) the first follow-up biopsy was the strongest predictor of disease resolution; and (4) patients whose first follow-up biopsy reveals stromal decidualization without response of the endometrial glands have a very low disease resolution rate. These factors, if validated in future studies, may assist clinicians in counseling patients regarding the success of therapy both before initiating treatment as well as after the first interval assessment biopsy.

Prospective Studies

There is limited prospective data regarding nonsurgical hormonal treatment of endometrial cancer. In 2001, Wang et al. reported a prospective study of hormonal treatment of endometrial cancer [68]. In this very small study, women with clinical stage I grade 1 endometrioid adenocarcinoma were prospectively entered into an IRB-approved trial of hormonal therapy. Nine patients were accrued to the trial over an 8-year period. Despite the prospective nature of the study, all patients did not receive the same therapy, though the majority were treated with megestrol acetate and tamoxifen. Eight of the nine patients achieved complete remission, though one of them did not initially respond to therapy and had to be treated with GnRH agonist and increased dose of megestrol acetate. Two patients had a total of three term pregnancies. However, four of the eight responders developed recurrent disease.

Niwa et al. presented a very small prospective study of 12 women <40 years with grade 1 endometrial cancer [69]. Ultrasound and MRI were both used to assess myometrial invasion and ovarian involvement. All patients were treated with medroxyprogesterone acetate continuously and all 12 underwent complete remission of disease. Of ten patients attempting pregnancy, five had six full-term deliveries. Eight patients had recurrence of disease, and one of these patients had metastatic disease to the ovary at the time of surgery.

Ushijima et al. published a prospective multicenter study of hormonal treatment of endometrial cancer and complex atypical hyperplasia in 2007 [70]. All women were treated with 600 mg of medroxyprogesterone acetate orally for 26 weeks followed by cyclic estrogen and progesterone therapy for 6 months. For those who desired conception, fertility treatment was started immediately. Response was assessed histologically at 8 weeks and 16 weeks, and at 26 weeks hysteroscopy and curettage were performed. A total of 45 patients were enrolled and eligible. Ages were 22–39 years (mean 31.7 years) and BMI was 16–32.7 (mean 22.8). Twenty-eight women had endometrial cancer: of these, 6 withdrew from the study and underwent hysterectomy. There were 12 complete responders (CR) for a 55 % CR rate. Seventeen patients had atypical hyperplasia, and 14 of these (82 %) had a CR at 26 weeks. During the surveillance period there was neoplastic recurrence in 47 % of the 30 patients, including 8 (57 %) of 14 with endometrial cancer and 6 (38 %) of 16 with atypical hyperplasia.

A prospective study from China was published in 2013 [71]. Women were eligible for entry if they had either grade 1 endometrial cancer or AH and were 40 years old or less, and if their tumor expressed the progesterone receptor (PR). Twenty-six eligible patients were enrolled in the study, 12 with AH and 14 with endometrial cancer. They were treated with oral megestrol acetate 160 mg daily for at least 12 weeks 18 patients achieved CR at 12 weeks (9 endometrial cancer, 9 AH) and another 3 patients achieved CR by 24 weeks (total 81 % CR rate).

There are currently two ongoing prospective trials for young women with CAH or endometrial cancer who want to preserve fertility listed in

clinicaltrials.gov (accessed February 2015) [72, 73].

Risks of Hormonal Therapy

Recurrence of Disease

Recurrence of endometrial neoplasia is a significant concern, particularly if progesterone treatment is stopped. The prospective study from Japan, for example, demonstrated a recurrence rate of 47 % between 7 and 36 months following treatment, prompting the authors to recommend close surveillance following treatment. Similarly, there was a 50 % disease recurrence rate of endometrial cancer reported in the series from Wang et al. [24]. Other studies have documented similar rates of disease recurrence [65, 71]. In some cases disease may recur even when treatment is continued. In these cases, the recurrence may be secondary to the downregulation of the progesterone receptor that occurs with prolonged progesterone treatment.

There remains the option of retreating once disease recurs if a patient desires to retain fertility. The largest retreatment series was reported from Korea in 2013 [74]. Forty-five patients developed recurrent endometrial neoplasia following complete response: recurrence was AH in 13 patients and grade 1 endometrial cancer in 20 patients. After retreatment with oral progesterone, 28 patients (85 %) had a second complete response in an average of 51 months (range 24–160 months).

Progression of Disease

Certainly, there is concern for progression of disease during the delay that occurs during hormonal therapy. It is conceivable that if the cancer being treated is not responsive to hormones and/or more definitive surgical therapy is delayed for 3 months, the stage of disease at the time of ultimate surgery could be higher. Kim et al. reported 3 of 21 initial responders to progesterone who experienced recurrent disease; one of these patients had evidence of metastatic disease at the time of her surgery. The authors raised the possibility of progesterone therapy delaying definitive surgical therapy, possibly resulting in the development of metastatic disease [75]. This patient was also the only one in the series with grade 2 disease, prompting the authors to suggest that only patients with grade 1 disease be considered for hormonal management.

There are several other case reports of patients whose disease has progressed following conservative therapy, in some cases resulting in cancer related mortality. In the case reported by Ferrandina et al., a 30-year-old woman was treated successfully for her grade 1 clinical stage IA endometrial cancer as documented by hysteroscopy and D&C [76]. Three months following resolution of her disease, she became pregnant and had a cesarean section at 36 weeks. Eight months later, she developed irregular bleeding and underwent definitive surgical therapy. She was diagnosed with stage IV poorly differentiated endometrial cancer and died of her disease.

Rubatt et al. reported a 40-year-old obese woman who underwent hormonal therapy for CAH [77]. The patient experienced complete regression and was compliant with follow-up. Two years following initial treatment she was diagnosed with a grade 2 endometrial cancer. At the time of surgery, she was found to have a stage IIIC grade 2 endometrial cancer with significant lymphovascular invasion within the myometrium and one positive pelvic lymph node. Kaku et al. reported 12 women with endometrial cancer who underwent hormonal therapy; 2 of 9 responders later developed relapse, and 1 of these had stage IIIC disease, with a positive obturator lymph node [78]. Kothari et al. reported a case of a 24-year-old woman treated with progestin who at the time of surgery was noted to have stage IV disease [79]. These reports and others point to the potential risk of converting a curable surgical problem into a life threatening illness by foregoing surgery in favor of fertility preservation.

It should be noted that there are a large number of small case reports, usually reporting

between 1 and 4 cases, of women with endometrial cancer who were treated with hormones and achieved pregnancy [80–89]. Most of them had grade 1 tumors that were extensively "clinically" staged with D&C, plus or minus hysteroscopy, CT and/or MRI, and laparoscopy. Many of these women were diagnosed during infertility evaluation and many required artificial reproductive technology (ART) to achieve pregnancy. One must consider when reading these reports the phenomenon of recall bias.

Any patient who chooses hormonal therapy over definitive surgical therapy should be counseled that surgical therapy is almost always curative for stage IA grade 1 cancers and that hormonal therapy as an alternative poses a theoretical risk of progression of disease to a stage that may expose the patient to the need for adjuvant therapy and the not insignificant risk of recurrent disease.

Risk of Metastases to the Ovary and/or Synchronous Ovarian Primary Tumors

There is a risk, though small, of endometrial cancer embolizing through the fallopian tube and metastasizing to the ovary. In the GOG staging study of clinical stage I endometrial cancer, this risk was 5 % [29]. Gross ovarian metastases can be ruled out via pelvic examination and/or pelvic ultrasound, but micrometastases cannot be demonstrated without histologic examination of the ovaries.

Recent literature has raised significant concerns regarding the risk of synchronous ovarian primary tumors in young women with endometrial cancer. The issue was raised by Walsh et al. in the context of considering preserving ovarian function in young women with endometrial cancer, removing the uterus but leaving the ovaries intact [90]. The authors reviewed 102 patients age 45 and younger that underwent hysterectomy for endometrial cancer. Twenty-six women in this series (25 %) had a coexisting ovarian malignancy, which were felt to be a synchronous ovarian primary in 23 cases. All ovarian tumors were epithelial, and all but one were endometrioid carcinomas. Eighteen of the 26 cases (69 %) occurred in women with grade 1 endometrial cancer. Twenty-six patients in this series underwent hormonal treatment for endometrial cancer prior to ultimate surgical management. Four of them (15 %) had ovarian involvement with cancer diagnosed at the time of their surgery and one had an ovarian tumor that was felt to be a synchronous ovarian primary. A population based study from Geneva reported more synchronous ovarian malignancies in young patients (14 % vs. 2 %): in this large series, 5 % of patients 40 years old or less had a synchronous ovarian cancer, compared to 23 % of women 41–45 years old [91]. In the Yale study, patients under age 45 whose surgery included removal of the ovaries had a significantly longer disease free survival but not overall survival and ovarian preservation had no significant influence on disease free survival in patients with grade 1 disease [16].

In contrast to these reports is the SEER report from Wright et al. that considered the safety of ovarian preservation in women with endometrial cancer [92]. In this series, SEER data from 1988 to 2004 for women less than or equal to 45 years of age was analyzed. A total of 402 women had ovarian preservation. In a multivariate analysis, ovarian preservation had no effect on either cancer specific or overall survival. The details of the ovarian cancers was not provided due to the nature of the study; the finding may be related to the low grade and early stage of most ovarian cancers diagnosed in this setting.

Two cases reported from Memorial Sloan Kettering illustrate this point [93]. The patients reported were 29 and 23 years old and strongly desired fertility preservation. When hormonal therapy failed, both women chose to undergo hysterectomy with ovarian preservation for the purposes of ovarian stimulation and surrogacy. Unfortunately, both women subsequently developed ovarian cancer: in both cases the tumors were histologically endometrioid and early stage.

Other authors have also reported a risk of synchronous ovarian primary cancer in patients with an endometrial cancer [7, 11, 12, 14, 94, 95]. Obviously, when considering hormonal

therapy, ovarian involvement needs to be carefully ruled out. Pelvic ultrasound may be the most useful modality to evaluate the ovaries for any abnormality and CA-125 can be used preoperatively as well [71]. It has also suggested the use of laparoscopy preoperatively to rule out ovarian involvement [96], though this is not a standard recommendation.

Risk of Tumor Recurrence During Pregnancy

Unfortunately, endometrial cancer recurrence has been documented during pregnancy. In one study, a lesion was interpreted to have been present during pregnancy, despite documentation of resolution of disease after treatment with hormones, and was diagnosed shortly after delivery [97]. Intuitively, one would think that high levels of progesterone achieved during pregnancy should be protective against recurrence of endometrial cancer, but this is not always the case.

Method of Treatment

There is no standardized agreed upon method for treating women with endometrial cancer with hormones. Most gynecologic oncologists choose megestrol acetate as a first choice, but doses and schedules are not standardized. Doses as low as 40 mg daily and as high as 160 mg four times daily have been reported. Medroxyprogesterone acetate, depo-medroxyprogesterone acetate, and combinations of tamoxifen and progesterone have also been suggested. While some authors suggest using cyclic therapy to induce a monthly withdrawal bleed, most advocate continuous treatment which ultimately results in an atrophic endometrium. Since progesterone is poorly tolerated by many women, with breast tenderness and weight gain being frequent complaints, it is probably best to use the lowest dose that will also be successful in reversing the neoplastic endometrium, though this lowest dose probably varies from woman to woman and likely its success is dependent on patient's BMI and tumor.

Several authors have suggested the use of a progesterone intrauterine device (IUD) as a means of treating the cancer with high doses of progesterone without the systemic side effects. In the study from Montz et al., women with clinical stage IA grade 1 endometrial cancer underwent hysteroscopy and curettage followed by placement of a progesterone IUD and resampling every 3 months [98]. Seven of 11 patients demonstrated complete response at 6 months and 6 of 8 at 12 months.

Dhar et al. performed a similar study using a levonorgestrel containing IUD [99]. Four women with grade 1 adenocarcinoma that expressed PR were treated with IUD; only one patient had a complete response within 6 months. However, this study did not exclude myometrial invasion prior to the treatment with IUD. In both studies, the majority of patients were postmenopausal and underwent hormonal treatment because it was felt that they were poor surgical candidates; thus, it is impossible to know whether a similar treatment regimen in premenopausal women would have similar outcome. Moreover, two women were reported to possibly have developed adenocarcinoma in the uterine isthmus while using a levonorgestrel IUD, suggesting that either the uterine cavity does not receive a uniform dose of progesterone, or that the cancer is not uniformly receptive to hormonal treatment [100]. In any case, the treatment results from systemic (by mouth) progestin or intrauterine progestin appear to be the same [101].

Once the treatment itself is chosen, appropriate follow-up of the patient is also not standardized. How frequently should the endometrium be resampled following treatment? How long should the treating clinician wait for complete response? Once complete response has been established, how should the patient then be followed to rule out recurrence? The appropriate treatment and follow-up course has not been established. It is clear, however, that responses may not be seen at the first 3-month resampling, and that the recurrence risk is high. It seems reasonable to suggest that patients be resampled

3 months after beginning hormonal therapy. If an incomplete response is documented, a further 3-month trial of treatment, perhaps with increased dose or different medication, may be appropriate. Once complete remission is established, pregnancy (if desired) should be aggressively pursued, with ART if required. If pregnancy is not desired, a "maintenance" hormonal treatment must be utilized to prevent recurrence. This maintenance therapy might consist of the birth control pill, monthly withdrawal bleeds with progesterone, or continuous progesterone therapy, either by mouth, intramuscular, or intrauterine.

Many women with endometrial cancer treated with progesterone will require ART to achieve pregnancy. In the study from Korea, 44 of 70 women used ART to achieve pregnancy; with a higher pregnancy rate (86 % vs. 50 %) and live birth rate (71 % vs. 42 %) than those patients who attempted natural pregnancy [23]. Since ART generates very high serum estradiol levels (which thereby put the patient at risk for recurrence if pregnancy is not achieved), many community in vitro fertility (IVF) programs may feel uncomfortable managing these patients. Moreover, many of these women are in the older range of reproductive age and therefore have lower success rates for IVF, perhaps requiring multiple attempts at ovulation induction to achieve pregnancy. These risks must be considered in the overall counseling of these patients when they are contemplating hormonal management for preservation of fertility.

Mechanisms of Hormone Receptor Action in Endometrial Cancer

The presence of PR in endometrial cancer does not guarantee response to progesterone. The simple notion of a generic progesterone receptor has been replaced over the last 10 years with a better understanding of the complexity of the PR and the mechanism of action of hormones on endometrial cancer. Nevertheless, currently there is no method to predict which cancers will regress with hormonal therapy and which will persist. Moreover, tumors may respond to progesterone therapy only partially, with persistence of disease in some areas of the uterus and response in others. While we have a general clinical sense that many CAH and endometrial cancers will respond to progesterone, the understanding of this response at the molecular level is rudimentary at best.

Most endometrioid adenocarcinomas express PR [102]. The lower grade tumors express PR more frequently, with a decrease in PR expression with increasing tumor grade [103–105]. However, there is a variable response to progesterone treatment within a single tumor and tumors can have both PR-positive and PR-negative areas [106–109]. Therefore, the presence of PR by immunohistochemistry does not reliably predict response to progesterone therapy. Furthermore, we now have more information regarding the complexity of the PR and the interactions between its two isoforms, PRA and PRB. Either the two isoforms have divergent responses or the ratio of the isoforms might be important [110–113]. There are also several cofactors and corepressors that can influence PR-mediated action [114–119]. The study of Arnett-Mansfield et al. illustrates the difficulty of utilizing immunohistochemistry and the presence or absence of receptor to predict response [120]. The authors studied PR isoforms in archived endometrial cancer tissue. Ninety-six percent of tumors expressed PR. Only 30 % of tumors expressed PRA alone, 42 % expressed both isoforms, and 28 % expressed PRB alone. PRB-only tumors had low levels of PR and those tumors that expressed both isoforms tended to express predominantly PRA. Based on their data, the authors hypothesized that loss of PRB resulted in the development of endometrial cancer. The finding of different expression of the isoforms has been supported by other groups (67, 70) [110, 113]. Other authors have suggested that it is the ratio of the isoforms that is most important (78) [121]. Thus, it is most likely that the ratio of PRA to PRB determines both the development of endometrial cancer and the ultimate response or lack thereof to progesterone treatment.

GOG211 was the first nontherapeutic preoperative trial in women with endometrial cancer

[122]. In this study, mainly postmenopausal women were registered, resulting in a lower treatment response than would be expected from a younger (premenopausal) population. After diagnosis of endometrial cancer by endometrial biopsy, patients were enrolled to receive Depo-medroxyprogesterone acetate 21–24 days prior to planned surgery. The biopsy and hysterectomy specimens were evaluated for estrogen and progesterone receptor expression, as well as other markers for proliferation and apoptosis. Fifty-nine women received treatment with progestin per protocol and had available slides. Only one complete histologic response was seen, and 37 tumors (87 %) had a partial response. PR and PRB were both significantly downregulated following treatment with progesterone. This downregulation of PR and PRB following treatment may contribute to later resistance to progesterone therapy.

As the presence of PR alone does not predict response to progesterone therapy, molecular markers of progesterone response that are measurable in paraffin-fixed tissue will be needed in the future to predict response of an individual tumor to progesterone therapy. Moreover, since different areas of each tumor may respond to treatment differently, careful monitoring of response will always be necessary.

Treatment of the Postmenopausal Woman with Progestin

Certain postmenopausal women will not be candidates for surgery for their endometrial cancer, most often due to medical comorbidities such as morbid obesity, diabetes, heart disease, etc. For those women with grade 1 non-invasive disease, progestin therapy may be a therapeutic option. There is very little data addressing the response rates of older women to progestin, but it has been documented that response rates for both CAH and endometrial cancer are lower in the post menopause than in the premenopause [95]. Further study is needed in this area.

Future Directions

As women in the USA continue to delay childbearing and as obesity rates rise, the numbers of women with endometrial cancer who wish to preserve their fertility will continue to increase. Counseling of these women regarding uterine preservation is limited by the lack of data and lack of standardized management schemas. Prospective trials are underway, seeking to establish a standard drug, dose, and schedule for progesterone therapy, and its appropriate monitoring. In order to establish a new standard of care in this setting, we require a better understanding at the molecular and genetic level of the mechanism of the different progesterone formulations on endometrial cancer at the level of the PR isoforms. It may be that a specific novel progesterone directed at one or the other PR isoforms will be the best treatment in the future, or perhaps directed therapy to each particular tumor depending upon that tumor's expression pattern of PR isoforms.

For the present time, any young woman with endometrial cancer wishing to be treated with progesterone in order to preserve fertility should be managed with the guidance of a gynecologic oncologist wherever possible and should be informed of all of the risks of less than standard of care treatment, including the not insignificant risk of progression of disease and potential development of ovarian synchronous primary tumors or ovarian metastases. Only women with grade 1 endometrioid adenocarcinomas and disease that is clinically felt to be confined to the endometrium with the best available radiologic modality should be considered for therapy. While the MGH study failed to identify any clinical or immunohistologic factors other than grade that are predictive of stage IA disease and thus predictive of successful hormonal therapy, other small studies have suggested histologic architectural complexity and high BMI to be predictive of treatment failure. It is however premature to use this data in counseling women against an attempt at conservative fertility sparing therapy if otherwise appropriate.

Patients who wish to proceed with progesterone therapy rather than surgery should be counseled that this therapy is not the standard of care treatment for endometrial cancer. Treating with less than the standard of care could potentially result in a young woman dying of a surgically curable disease.

Conclusions

To pursue primary hormonal therapy of endometrial cancer, the following steps are required:

- Confirm that the tumor is endometrioid and grade 1 by pathologic review. If diagnosis was made by endometrial biopsy, perform D&C to ensure complete sampling of the endometrial cavity.
- Obtain a careful medical history and perform physical examination with particular attention to family history. A family history that suggests Lynch syndrome should result in genetic counseling and possible testing as patient is at increased risk for colon and ovarian cancer. Attention should also be paid to medical history that might complicate future pregnancies (obesity, diabetes, hypertension). Microsatellite instability testing may be performed on endometrial biopsy samples to assist in screening for genetic syndromes.
- MRI and/or ultrasound should be performed to rule out adnexal metastases and evaluate for myometrial invasion.

If the tumor is well sampled and grade 1 with no evidence of extrauterine disease or myometrial invasion, the patient should undergo:

- Informed counseling, preferably with a gynecologic oncologist.
- Treatment with progesterone, either continuous or cyclic, or via intrauterine device.
- Resampling in 3 months to assess response.
- If resolution of disease: patient should be encouraged to achieve pregnancy quickly. Many of these patients will require ART.
- If incomplete resolution of disease: patient may be continued on treatment for another 3 months and rebiopsied. The clinician may also consider another medication regimen or a higher dose of the same formulation and resample in 3 months.
- Once childbearing is complete or if treatment fails, the patient should be counseled for definitive surgical therapy consisting of TAH–BSO with lymphadenectomy as appropriate. Certain patients may be candidates for ovarian preservation but this should be done with caution and appropriate counseling.

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Can J Clin. 2014;64(1):9–29.
2. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynaecol Obstet. 2009;105(2):103–4.
3. Lajer H, Elnegaard S, Christensen RD, Ortoft G, Schledermann DE, Mogensen O. Survival after stage IA endometrial cancer; can follow-up be altered? A prospective nationwide Danish survey. Acta Obstet Gynecol Scand. 2012;91(8):976–82.
4. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review. National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2011/ , based on November 2013 SEER data submission, posted to the SEER web site, April 2014. 1975-2011
5. Peterson EP. Endometrial carcinoma in young women. A clinical profile. Obstet Gynecol. 1968;31 (5):702–7.
6. Kempson RL, Pokorny GE. Adenocarcinoma of the endometrium in women aged forty and younger. Cancer. 1968;21(4):650–62.
7. Crissman JD, Azoury RS, Barnes AE, Schellhas HF. Endometrial carcinoma in women 40 years of age or younger. Obstet Gynecol. 1981;57 (6):699–704.
8. Gallup DG, Stock RJ. Adenocarcinoma of the endometrium in women 40 years of age or younger. Obstet Gynecol. 1984;64(3):417–20.
9. Farhi DC, Nosanchuk J, Silverberg SG. Endometrial adenocarcinoma in women under 25 years of age. Obstet Gynecol. 1986;68(6):741–5.
10. Jeffery JD, Taylor R, Robertson DI, Stuart GC. Endometrial carcinoma occurring in patients under the age of 45 years. Am J Obstet Gynecol. 1987;156(2):366–70.
11. Gitsch G, Hanzal E, Jensen D, Hacker NF. Endometrial cancer in premenopausal women

45 years and younger. Obstet Gynecol. 1995;85 (4):504–8.
12. Evans-Metcalf ER, Brooks SE, Reale FR, Baker SP. Profile of women 45 years of age and younger with endometrial cancer. Obstet Gynecol. 1998;91 (3):349–54.
13. Soliman PT, Oh JC, Schmeler KM, et al. Risk factors for young premenopausal women with endometrial cancer. Obstet Gynecol. 2005;105(3):575–80.
14. Duska LR, Garrett A, Rueda BR, Haas J, Chang Y, Fuller AF. Endometrial cancer in women 40 years old or younger. Gynecol Oncol. 2001;83(2):388–93.
15. Lee NK, Cheung MK, Shin JY, et al. Prognostic factors for uterine cancer in reproductive-aged women. Obstet Gynecol. 2007;109(3):655–62.
16. Richter CE, Qian B, Martel M, et al. Ovarian preservation and staging in reproductive-age endometrial cancer patients. Gynecol Oncol. 2009;114 (1):99–104.
17. Polednak AP. Trends in incidence rates for obesity-associated cancers in the US. Cancer Detect Prev. 2003;27(6):415–21.
18. Reeves GK, Pirie K, Beral V, et al. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. BMJ. 2007;335 (7630):1134.
19. Havrilesky LJ, Maxwell GL, Myers ER. Cost-effectiveness analysis of annual screening strategies for endometrial cancer. Am J Obstet Gynecol. 2009;200(6):640, e641–e648.
20. Kwon JS, Lu KH. Cost-effectiveness analysis of endometrial cancer prevention strategies for obese women. Obstet Gynecol. 2008;112(1):56–63.
21. Rose PG. Endometrial carcinoma. N Engl J Med. 1996;335(9):640–9.
22. Schmeler KM, Soliman PT, Sun CC, Slomovitz BM, Gershenson DM, Lu KH. Endometrial cancer in young, normal-weight women. Gynecol Oncol. 2005;99(2):388–92.
23. Park JY, Seong SJ, Kim TJ, et al. Pregnancy outcomes after fertility-sparing management in young women with early endometrial cancer. Obstet Gynecol. 2013;121(1):136–42.
24. Wang CJ, Chao A, Yang LY, et al. Fertility-preserving treatment in young women with endometrial adenocarcinoma: a long-term cohort study. Int J Gynecol Cancer. 2014;24(4):718–28.
25. Lu KH, Dinh M, Kohlmann W, et al. Gynecologic cancer as a "sentinel cancer" for women with hereditary nonpolyposis colorectal cancer syndrome. Obstet Gynecol. 2005;105(3):569–74.
26. Kurman RJ, Norris HJ. Evaluation of criteria for distinguishing atypical endometrial hyperplasia from well-differentiated carcinoma. Cancer. 1982;49(12):2547–59.
27. Zaino RJ, Kauderer J, Trimble CL, et al. Reproducibility of the diagnosis of atypical endometrial hyperplasia: a Gynecologic Oncology Group study. Cancer. 2006;106(4):804–11.
28. Trimble CL, Kauderer J, Zaino R, et al. Concurrent endometrial carcinoma in women with a biopsy diagnosis of atypical endometrial hyperplasia: a Gynecologic Oncology Group study. Cancer. 2006;106(4):812–9.
29. Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer: a Gynecologic Oncology Group study. Cancer. 1987;60 (8 Suppl):2035–41.
30. Walker JL, Piedmonte MR, Spirtos NM, et al. Laparoscopy compared with laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group study LAP2. J Clin Oncol. 2009;27(32):5331–6.
31. Cowles TA, Magrina JF, Masterson BJ, Capen CV. Comparison of clinical and surgical-staging in patients with endometrial carcinoma. Obstet Gynecol. 1985;66(3):413–6.
32. Daniel AG, Peters 3rd WA. Accuracy of office and operating room curettage in the grading of endometrial carcinoma. Obstet Gynecol. 1988;71 (4):612–4.
33. Eltabbakh GH, Shamonki J, Mount SL. Surgical stage, final grade, and survival of women with endometrial carcinoma whose preoperative endometrial biopsy shows well-differentiated tumors. Gynecol Oncol. 2005;99(2):309–12.
34. DelMaschio A, Vanzulli A, Sironi S, et al. Estimating the depth of myometrial involvement by endometrial carcinoma: efficacy of transvaginal sonography vs MR imaging. AJR Am J Roentgenol. 1993;160(3):533–8.
35. Gordon AN, Fleischer AC, Dudley BS, et al. Preoperative assessment of myometrial invasion of endometrial adenocarcinoma by sonography (US) and magnetic resonance imaging (MRI). Gynecol Oncol. 1989;34(2):175–9.
36. Kim SH, Kim HD, Song YS, Kang SB, Lee HP. Detection of deep myometrial invasion in endometrial carcinoma: comparison of transvaginal ultrasound, CT, and MRI. J Comput Assist Tomogr. 1995;19(5):766–72.
37. Zerbe MJ, Bristow R, Grumbine FC, Montz FJ. Inability of preoperative computed tomography scans to accurately predict the extent of myometrial invasion and extracorporal spread in endometrial cancer. Gynecol Oncol. 2000;78(1):67–70.
38. Hardesty LA, Sumkin JH, Hakim C, Johns C, Nath M. The ability of helical CT to preoperatively stage endometrial carcinoma. AJR Am J Roentgenol. 2001;176(3):603–6.
39. Frei KA, Kinkel K. Staging endometrial cancer: role of magnetic resonance imaging. J Magn Res Imag JMRI. 2001;13(6):850–5.
40. Chung HH, Kang SB, Cho JY, et al. Accuracy of MR imaging for the prediction of myometrial invasion of endometrial carcinoma. Gynecol Oncol. 2007;104 (3):654–9.

41. Nakao Y, Yokoyama M, Hara K, et al. MR imaging in endometrial carcinoma as a diagnostic tool for the absence of myometrial invasion. Gynecol Oncol. 2006;102(2):343–7.
42. Yamashita Y, Harada M, Sawada T, Takahashi M, Miyazaki K, Okamura H. Normal uterus and FIGO stage I endometrial carcinoma: dynamic gadolinium-enhanced MR imaging. Radiology. 1993;186 (2):495–501.
43. Sironi S, Colombo E, Villa G, et al. Myometrial invasion by endometrial carcinoma: assessment with plain and gadolinium-enhanced MR imaging. Radiology. 1992;185(1):207–12.
44. Scoutt LM, McCarthy SM, Flynn SD, et al. Clinical stage I endometrial carcinoma: pitfalls in preoperative assessment with MR imaging. Work in progress. Radiology. 1995;194(2):567–72.
45. Lee EJ, Byun JY, Kim BS, Koong SE, Shinn KS. Staging of early endometrial carcinoma: assessment with T2-weighted and gadolinium-enhanced T1-weighted MR imaging. Radiographics. 1999;19 (4):937–45. discussion 946–937.
46. Minderhoud-Bassie W, Treurniet FE, Koops W, Chadha-Ajwani S, Hage JC, Huikeshoven FJ. Magnetic resonance imaging (MRI) in endometrial carcinoma; preoperative estimation of depth of myometrial invasion. Acta Obstet Gynecol Scand. 1995;74(10):827–31.
47. Suh DS, Kim JK, Kim KR, et al. Reliability of magnetic resonance imaging in assessing myometrial invasion absence in endometrial carcinoma. Acta Obstet Gynecol Scand. 2009;88(9):990–3.
48. Hricak H, Stern JL, Fisher MR, Shapeero LG, Winkler ML, Lacey CG. Endometrial carcinoma staging by MR imaging. Radiology. 1987;162 (2):297–305.
49. Ito K, Matsumoto T, Nakada T, Nakanishi T, Fujita N, Yamashita H. Assessing myometrial invasion by endometrial carcinoma with dynamic MRI. J Comput Assist Tomogr. 1994;18(1):77–86.
50. Kinkel K, Kaji Y, Yu KK, et al. Radiologic staging in patients with endometrial cancer: a meta-analysis. Radiology. 1999;212(3):711–8.
51. Sanjuan A, Escaramis G, Ayuso JR, et al. Role of magnetic resonance imaging and cause of pitfalls in detecting myometrial invasion and cervical involvement in endometrial cancer. Arch Gynecol Obstet. 2008;278(6):535–9.
52. Joja I, Asakawa M, Asakawa T, et al. Endometrial carcinoma: dynamic MRI with turbo-FLASH technique. J Comput Assist Tomogr. 1996;20(6):878–87.
53. Saez F, Urresola A, Larena JA, et al. Endometrial carcinoma: assessment of myometrial invasion with plain and gadolinium-enhanced MR imaging. J Magn Res Imag JMRI. 2000;12(3):460–6.
54. Savci G, Ozyaman T, Tutar M, Bilgin T, Erol O, Tuncel E. Assessment of depth of myometrial invasion by endometrial carcinoma: comparison of T2-weighted SE and contrast-enhanced dynamic GRE MR imaging. Eur Radiol. 1998;8(2):218–23.
55. Seki H, Kimura M, Sakai K. Myometrial invasion of endometrial carcinoma: assessment with dynamic MR and contrast-enhanced T1-weighted images. Clin Radiol. 1997;52(1):18–23.
56. Ben-Shachar I, Vitellas KM, Cohn DE. The role of MRI in the conservative management of endometrial cancer. Gynecol Oncol. 2004;93(1):233–7.
57. Frei KA, Kinkel K, Bonel HM, Lu Y, Zaloudek C, Hricak H. Prediction of deep myometrial invasion in patients with endometrial cancer: clinical utility of contrast-enhanced MR imaging-a meta-analysis and Bayesian analysis. Radiology. 2000;216(2):444–9.
58. Simpson AN, Feigenberg T, Clarke BA, et al. Fertility sparing treatment of complex atypical hyperplasia and low grade endometrial cancer using oral progestin. Gynecol Oncol. 2014;133(2):229–33.
59. Ramirez PT, Frumovitz M, Bodurka DC, Sun CC, Levenback C. Hormonal therapy for the management of grade 1 endometrial adenocarcinoma: a literature review. Gynecol Oncol. 2004;95(1):133–8.
60. Gotlieb WH, Beiner ME, Shalmon B, et al. Outcome of fertility-sparing treatment with progestins in young patients with endometrial cancer. Obstet Gynecol. 2003;102(4):718–25.
61. Gunderson CC, Fader AN, Carson KA, Bristow RE. Oncologic and reproductive outcomes with progestin therapy in women with endometrial hyperplasia and grade 1 adenocarcinoma: a systematic review. Gynecol Oncol. 2012;125(2):477–82.
62. Koskas M, Uzan J, Luton D, Rouzier R, Darai E. Prognostic factors of oncologic and reproductive outcomes in fertility-sparing management of endometrial atypical hyperplasia and adenocarcinoma: systematic review and meta-analysis. Fertil Steril. 2014;101(3):785–94.
63. Bokhman JV, Chepick OF, Volkova AT, Vishnevsky AS. Can primary endometrial carcinoma stage I be cured without surgery and radiation therapy? Gynecol Oncol. 1985;20(2):139–55.
64. Randall TC, Kurman RJ. Progestin treatment of atypical hyperplasia and well-differentiated carcinoma of the endometrium in women under age 40. Obstet Gynecol. 1997;90(3):434–40.
65. Park JY, Kim DY, Kim JH, et al. Long-term oncologic outcomes after fertility-sparing management using oral progestin for young women with endometrial cancer (KGOG 2002). Eur J Cancer. 2013;49 (4):868–74.
66. Park JY, Kim DY, Kim TJ, et al. Hormonal therapy for women with stage IA endometrial cancer of all grades. Obstet Gynecol. 2013;122(1):7–14.
67. Penner KR, Dorigo O, Aoyama C, et al. Predictors of resolution of complex atypical hyperplasia or grade 1 endometrial adenocarcinoma in premenopausal women treated with progestin therapy. Gynecol Oncol. 2012;124(3):542–8.

68. Wang CB, Wang CJ, Huang HJ, et al. Fertility-preserving treatment in young patients with endometrial adenocarcinoma. Cancer. 2002;94 (8):2192–8.
69. Niwa K, Tagami K, Lian Z, Onogi K, Mori H, Tamaya T. Outcome of fertility-preserving treatment in young women with endometrial carcinomas. BJOG. 2005;112(3):317–20.
70. Ushijima K, Yahata H, Yoshikawa H, et al. Multicenter phase II study of fertility-sparing treatment with medroxyprogesterone acetate for endometrial carcinoma and atypical hyperplasia in young women. J Clin Oncol. 2007;25(19):2798–803.
71. Shan BE, Ren YL, Sun JM, et al. A prospective study of fertility-sparing treatment with megestrol acetate following hysteroscopic curettage for well-differentiated endometrioid carcinoma and atypical hyperplasia in young women. Arch Gynecol Obstet. 2013;288(5):1115–23.
72. NCT00788671. Levonorgestrel Intrauterine Device (IUD) to Treat Complex Atypical Hyperplasia (CAH) and Grade 1 Endometrioid Endometrial Carcinoma (G1EEC). (Sponsor: MD Anderson PI: Shannon Westin, MD).
73. NCT01594879. Treatment With Medroxyprogesterone Acetate Plus LNG-IUS in Young Women With Early Stage Endometrial Cancer.Sponsor: Korean Gynecologic Oncology Group PI: Seok Ju Soeng, MD.
74. Park JY, Lee SH, Seong SJ, et al. Progestin re-treatment in patients with recurrent endometrial adenocarcinoma after successful fertility-sparing management using progestin. Gynecol Oncol. 2013;129(1):7–11.
75. Kim YB, Holschneider CH, Ghosh K, Nieberg RK, Montz FJ. Progestin alone as primary treatment of endometrial carcinoma in premenopausal women. Report of seven cases and review of the literature. Cancer. 1997;79(2):320–7.
76. Ferrandina G, Zannoni GF, Gallotta V, Foti E, Mancuso S, Scambia G. Progression of conservatively treated endometrial carcinoma after full term pregnancy: a case report. Gynecol Oncol. 2005;99 (1):215–7.
77. Rubatt JM, Slomovitz BM, Burke TW, Broaddus RR. Development of metastatic endometrial endometrioid adenocarcinoma while on progestin therapy for endometrial hyperplasia. Gynecol Oncol. 2005;99(2):472–6.
78. Kaku T, Yoshikawa H, Tsuda H, et al. Conservative therapy for adenocarcinoma and atypical endometrial hyperplasia of the endometrium in young women: central pathologic review and treatment outcome. Cancer Lett. 2001;167(1):39–48.
79. Kothari R, Seamon L, Cohn D, Fowler J, O'Malley DM. Stage IV endometrial cancer after failed conservative management: a case report. Gynecol Oncol. 2008;111(3):579–82.
80. Ogawa S, Koike T, Shibahara H, et al. Assisted reproductive technologies in conjunction with conservatively treated endometrial adenocarcinoma. A case report. Gynecol Obstet Investig. 2001;51 (3):214–6.
81. Jobo T, Imai M, Kawaguchi M, Kenmochi M, Kuramoto H. Successful conservative treatment of endometrial carcinoma permitting subsequent pregnancy: report of two cases. Eur J Gynaecol Oncol. 2000;21(2):119–22.
82. Sardi J, Anchezar Henry JP, Paniceres G, Gomez Rueda N, Vighi S. Primary hormonal treatment for early endometrial carcinoma. Eur J Gynaecol Oncol. 1998;19(6):565–8.
83. Shibahara H, Shigeta M, Toji H, et al. Successful pregnancy in an infertile patient with conservatively treated endometrial adenocarcinoma after transfer of embryos obtained by intracytoplasmic sperm injection. Hum Reprod. 1999;14(7):1908–11.
84. Kung FT, Chen WJ, Chou HH, Ko SF, Chang SY. Conservative management of early endometrial adenocarcinoma with repeat curettage and hormone therapy under assistance of hysteroscopy and laparoscopy. Hum Reprod. 1997;12(8):1649–53.
85. Mazzon I, Corrado G, Morricone D, Scambia G. Reproductive preservation for treatment of stage IA endometrial cancer in a young woman: hysteroscopic resection. Int J Gynecol Cancer. 2005;15 (5):974–8.
86. Yarali H, Bozdag G, Aksu T, Ayhan A. A successful pregnancy after intracytoplasmic sperm injection and embryo transfer in a patient with endometrial cancer who was treated conservatively. Fertil Steril. 2004;81(1):214–6.
87. Nakao Y, Nomiyama M, Kojima K, Matsumoto Y, Yamasaki F, Iwasaka T. Successful pregnancies in 2 infertile patients with endometrial adenocarcinoma. Gynecol Obstet Investig. 2004;58 (2):68–71.
88. Pinto AB, Gopal M, Herzog TJ, Pfeifer JD, Williams DB. Successful in vitro fertilization pregnancy after conservative management of endometrial cancer. Fertil Steril. 2001;76(4):826–9.
89. Kimmig R, Strowitzki T, Muller-Hocker J, Kurzl R, Korell M, Hepp H. Conservative treatment of endometrial cancer permitting subsequent triplet pregnancy. Gynecol Oncol. 1995;58(2):255–7.
90. Walsh C, Holschneider C, Hoang Y, Tieu K, Karlan B, Cass I. Coexisting ovarian malignancy in young women with endometrial cancer. Obstet Gynecol. 2005;106(4):693–9.
91. Navarria I, Usel M, Rapiti E, et al. Young patients with endometrial cancer: how many could be eligible for fertility-sparing treatment? Gynecol Oncol. 2009;114(3):448–51.

92. Wright JD, Buck AM, Shah M, Burke WM, Schiff PB, Herzog TJ. Safety of ovarian preservation in premenopausal women with endometrial cancer. J Clin Oncol. 2009;27(8):1214–9.
93. Zivanovic O, Carter J, Kauff ND, Barakat RR. A review of the challenges faced in the conservative treatment of young women with endometrial carcinoma and risk of ovarian cancer. Gynecol Oncol. 2009;115(3):504–9.
94. Shamshirsaz AA, Withiam-Leitch M, Odunsi K, Baker T, Frederick PJ, Lele S. Young patients with endometrial carcinoma selected for conservative treatment: a need for vigilance for synchronous ovarian carcinomas, case report and literature review. Gynecol Oncol. 2007;104(3):757–60.
95. Zaino R, Whitney C, Brady MF, DeGeest K, Burger RA, Buller RE. Simultaneously detected endometrial and ovarian carcinomas—a prospective clinicopathologic study of 74 cases: a Gynecologic Oncology Group study. Gynecol Oncol. 2001;83 (2):355–62.
96. Morice P, Fourchotte V, Sideris L, Gariel C, Duvillard P, Castaigne D. A need for laparoscopic evaluation of patients with endometrial carcinoma selected for conservative treatment. Gynecol Oncol. 2005;96(1):245–8.
97. Mitsushita J, Toki T, Kato K, Fujii S, Konishi I. Endometrial carcinoma remaining after term pregnancy following conservative treatment with medroxyprogesterone acetate. Gynecol Oncol. 2000;79(1):129–32.
98. Montz FJ, Bristow RE, Bovicelli A, Tomacruz R, Kurman RJ. Intrauterine progesterone treatment of early endometrial cancer. Am J Obstet Gynecol. 2002;186(4):651–7.
99. Dhar KK, NeedhiRajan T, Koslowski M, Woolas RP. Is levonorgestrel intrauterine system effective for treatment of early endometrial cancer? Report of four cases and review of the literature. Gynecol Oncol. 2005;97(3):924–7.
100. Jones K, Georgiou M, Hyatt D, Spencer T, Thomas H. Endometrial adenocarcinoma following the insertion of a Mirena IUCD. Gynecol Oncol. 2002;87 (2):216–8.
101. Hubbs JL, Saig RM, Abaid LN, Bae-Jump VL, Gehrig PA. Systemic and local hormone therapy for endometrial hyperplasia and early adenocarcinoma. Obstet Gynecol. 2013;121(6):1172–80.
102. Jeon YT, Park IA, Kim YB, et al. Steroid receptor expressions in endometrial cancer: clinical significance and epidemiological implication. Cancer Lett. 2006;239(2):198–204.
103. Ehrlich CE, Young PC, Cleary RE. Cytoplasmic progesterone and estradiol receptors in normal, hyperplastic, and carcinomatous endometria: therapeutic implications. Am J Obstet Gynecol. 1981;141 (5):539–46.
104. Ehrlich CE, Young PC, Stehman FB, Sutton GP, Alford WM. Steroid receptors and clinical outcome in patients with adenocarcinoma of the endometrium. Am J Obstet Gynecol. 1988;158 (4):796–807.
105. Creasman WT, Soper JT, McCarty Jr KS, McCarty Sr KS, Hinshaw W, Clarke-Pearson DL. Influence of cytoplasmic steroid receptor content on prognosis of early stage endometrial carcinoma. Am J Obstet Gynecol. 1985;151(7):922–32.
106. Benraad TJ, Friberg LG, Koenders AJ, Kullander S. Do estrogen and progesterone receptors (E2R and PR) in metastasizing endometrial cancers predict the response to gestagen therapy? Acta Obstet Gynecol Scand. 1980;59(2):155–9.
107. Creasman WT, McCarty Sr KS, Barton TK, McCarty Jr KS. Clinical correlates of estrogen- and progesterone-binding proteins in human endometrial adenocarcinoma. Obstet Gynecol. 1980;55(3):363–70.
108. Martin PM, Rolland PH, Gammerre M, Serment H, Toga M. Estradiol and progesterone receptors in normal and neoplastic endometrium: correlations between receptors, histopathological examinations and clinical responses under progestin therapy. Inter J Can. 1979;23(3):321–9.
109. Kauppila A, Kujansuu E, Vihko R. Cytosol estrogen and progestin receptors in endometrial carcinoma of patients treated with surgery, radiotherapy, and progestin. Clinical correlates. Cancer. 1982;50 (10):2157–62.
110. Smid-Koopman E, Kuhne LC, Hanekamp EE, et al. Progesterone-induced inhibition of growth and differential regulation of gene expression in PRA- and/or PRB-expressing endometrial cancer cell lines. J Soc Gynecol Investig. 2005;12 (4):285–92.
111. Hanekamp EE, Gielen SC, Smid-Koopman E, et al. Consequences of loss of progesterone receptor expression in development of invasive endometrial cancer. Clin Cancer Res. 2003;9(11):4190–9.
112. Smid-Koopman E, Blok LJ, Kuhne LC, et al. Distinct functional differences of human progesterone receptors A and B on gene expression and growth regulation in two endometrial carcinoma cell lines. J Soc Gynecol Investig. 2003;10 (1):49–57.
113. Miyamoto T, Watanabe J, Hata H, et al. Significance of progesterone receptor-A and -B expressions in endometrial adenocarcinoma. J Steroid Biochem Mol Biol. 2004;92(3):111–8.
114. Conneely OM. Perspective: female steroid hormone action. Endocrinology. 2001;142(6):2194–9.
115. Conneely OM, Lydon JP. Progesterone receptors in reproduction: functional impact of the A and B isoforms. Steroids. 2000;65(10–11):571–7.
116. Conneely OM, Mulac-Jericevic B, Lydon JP, De Mayo FJ. Reproductive functions of the progesterone receptor isoforms: lessons from

knock-out mice. Mol Cell Endocrinol. 2001;179 (1–2):97–103.
117. Rowan BG, O'Malley BW. Progesterone receptor coactivators. Steroids. 2000;65(10–11):545–9.
118. Spitz IM, Coelingh Bennink HJ. Progesterone receptor modulators at the start of a new millennium. Steroids. 2000;65(10–11):837–8.
119. Bouchard P. Progesterone and the progesterone receptor. J Reprod Med. 1999;44(2 Suppl):153–7.
120. Arnett-Mansfield RL, deFazio A, Wain GV, et al. Relative expression of progesterone receptors A and B in endometrioid cancers of the endometrium. Cancer Res. 2001;61(11):4576–82.
121. Dai D, Kumar NS, Wolf DM, Leslie KK. Molecular tools to reestablish progestin control of endometrial cancer cell proliferation. Am J Obstet Gynecol. 2001;184(5):790–7.
122. Zaino RJ, Brady WE, Todd W, et al. Histologic effects of medroxyprogesterone acetate on endometrioid endometrial adenocarcinoma: a Gynecologic Oncology Group study. Int J Gynecol Pathol. 2014;33(6):543–53.