Progestins in the Fertility-Sparing Treatment and Retreatment of Patients With Primary and Recurrent Endometrial Cancer

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Endometrial cancer • Fertility-sparing • Conservative • Progestin

ABSTRACT

Endometrial cancer is the most common gynecologic cancer in developed countries. Approximately 3%–14% of endometrial cancers are diagnosed in young women under 40 who want to preserve their fertility. The incidence of endometrial cancer in this age group is increasing, for which fertility-sparing therapy is increasingly used because it is one of the most important quality of life issues in these women. Progestin therapy is the most common type of fertility-sparing therapy. In this review, the most up-to-date findings regarding fertility-sparing progestin therapy for young women with primary and recurrent endometrial cancer is addressed in terms of diagnosis, treatment, follow-up, and oncologic and reproductive outcomes. Fertility-sparing progestin therapy is highly effective in selected young women with primary and recurrent endometrial cancer. The selection of appropriate patients through comprehensive pretreatment evaluation is of paramount importance to achieve the best outcomes without compromising survival. Because of the high rate of recurrence after successful fertility-sparing therapy, close surveillance is mandatory, and prophylactic hysterectomy is the best option for patients who have completed family planning. Pregnancy outcomes are very promising with the aid of assisted reproductive technologies. Continuous daily oral medroxyprogesterone acetate and megestrol acetate are the preferred progestins for fertility-sparing therapy, but future studies should be performed to determine the optimal dose and treatment duration of these agents. The Oncologist 2015; 20:270–278

Implications for Practice: In young women with endometrial cancer, the cure rate is very high. Therefore, the efficacy of treatment should not be limited to the oncologic outcomes. The quality-of-life issue is as important as oncologic outcomes in these patients. Fertility preservation is one of the most important quality-of-life issues. Based on the results of numerous studies, fertility-sparing progestin therapy can be safely performed in endometrioid adenocarcinoma confined to the endometrium. It also can be reasonably recommended to selected women with more advanced disease and recurrent disease. However, careful follow-up is important because of the high rate of recurrence.

INTRODUCTION

Endometrial cancer is the most common gynecologic malignancy in Western countries [1, 2]. In the U.S., 49,560 new endometrial cancer cases and 8,190 deaths from endometrial cancer are projected to occur in 2013 [2]. In Eastern countries, the incidence of endometrial cancer is rapidly increasing, and it will be the most common gynecologic malignancy in the near future [3–5]. Endometrial cancer is a disease of perimenopausal women. However, approximately 3%–14% of endometrial cancer cases are diagnosed in women equal to or under 40 years of age who want to preserve their fertility [6, 7]. Endometrial cancers diagnosed at this age group are increasing in frequency and are typically early-stage, well-differentiated, endometrioid type adenocarcinomas [8, 9]. Hence, the incidence of myometrial invasion or lymph node metastasis is very rare in these cases [10, 11]. Because the cure rate is very high for endometrial cancer diagnosed at this age group, quality of life is as important as survival outcomes in these patients, and the preservation of fertility is one of the most important quality of life issues. Fertility-sparing management using various agents has thus been increasingly adopted as an alternative treatment.

Current fertility-sparing treatment modalities mainly comprise hormonal therapies involving progestins [12–16], progestin-releasing intrauterine devices [17–21], natural progesterone [22], oral contraceptives [23], selective estrogen receptor modulators [24–26], gonadotropin-releasing hormone...
agonist [24, 27], and aromatase inhibitors [28]. Of these treatments, progestin therapy is the most commonly used, and its efficacy is well-known compared with other treatment modalities. We here review the most recent findings for fertility-sparing management with progestin in young women with early endometrial cancer who want to preserve their fertility.

Materials and Methods

We performed a Medline search of articles published in English between January 1969 and September 2013 with the key words: “endometrial cancer,” “fertility-sparing,” “fertility preservation,” “conservative management,” and “progestin.” We identified further articles from the bibliographies of these publications including case reports, case series, original articles, review articles, and meta-analyses. The most up-to-date findings regarding diagnosis, treatment, oncologic and reproductive outcomes, and follow-up after fertility-sparing progestin therapy in young women with primary or recurrent reproductive outcomes, and follow-up after fertility-sparing progestin therapy were extracted from these reports.

Results

Progestosterone is a steroid hormone that opposes estrogen-driven growth and carcinogenesis in the endometrium. Excessive estrogen stimulation, which is not opposed by progesterone, will cause the development of endometrial hyperplasia or cancer. The mechanism of the anticancer effect of progesterone has been studied in women who were treated with progestin, xenograft models, and various cell lines. Progestins are made of synthetic progesterone and have been used for hormone therapy in women with endometrial hyperplasia or cancer. Progestin was previously considered to exert anticancer effects through downregulation of estrogen receptors and activation of enzymes involved in estrogen metabolism [29]. Recently, it is considered that the anticancer effect of progesterin is also exerted by involving cell cycle regulation by cyclin-dependent kinase, and antioncogene is an important factor for this process [29]. Progestin is known to enhance p27 expression, resulting in inhibition of cyclin E-Cdk2 function and suppression of the cell cycle [30].

Indications for Fertility-Sparing Progestin Therapy

The selection of endometrial cancer patients for whom fertility-sparing progestin therapy is appropriate is of paramount importance to achieve the best outcomes. In almost all relevant studies on this issue, fertility-sparing progestin therapy has been recommended for patients with presumed early-stage, well-differentiated, endometrioid type endometrial adenocarcinoma with no evidence of myometrial invasion or extraterine spread. According to the revised International Federation of Obstetrics and Gynecology staging system (2009), stage IA (confined to endometrium), grade 1 endometrioid adenocarcinoma cases are eligible for fertility-sparing progestin therapy.

It is important that well-differentiated tumors are verified and documented by an experienced gynecologic pathologist. Well-differentiated tumors have a very low risk of myometrial invasion and extraterine spread including lymph node, ovarian, or peritoneal metastasis [10, 31]. In addition, well-differentiated tumor cells are more likely to express progesterone receptors and therefore respond to progestin therapy [32]. The absence of myometrial invasion is also an important clinical aspect of endometrioid adenocarcinoma and implies a very low risk of extraterine spread [10, 11]. If these two criteria are met, the risk of extraterine disease is likely to be extremely rare, a positive response to progestin therapy is expected, and fertility-sparing progestin therapy can be safely recommended [10, 11].

Well-differentiated tumor cells are more likely to express progesterone receptors and therefore respond to progestin therapy. Navarria et al. [33] have reported the estimated number of patients who may need fertility-sparing progestin therapy in a population-based population as a rate of 0.3 in 100,000 women for these criteria. However, because the incidence of young women with endometrial cancer is increasing, as is the number of women who want to delay having children until their late 30s, the future need for fertility-sparing progestin therapy will necessarily increase [34].

Pretreatment Evaluation

To reduce the incidence of life-threatening sequelae, a comprehensive pretreatment evaluation to select appropriate patients for progestin therapy without compromising curability is vital. Careful history taking and physical examination should be carried out to obtain possible clues for extraterine spread of the disease. To assess the risk of familial cancer, careful family history taking and an appropriate genetic work-up are required. Endometrial cancer diagnosed in young women harbors the additional risk of cancers associated with the Lynch/hereditary nonpolyposis colorectal cancer (HNPPC) syndrome, as well as synchronous or metachronous ovarian cancers occurring outside the setting of Lynch/HNPPC syndrome. Because patients with endometrial cancer diagnosed prior to age 50 will have a risk greater than 5%–10% of having an inherited predisposition to a Lynch/HNPPC syndrome, genetic counseling may play an important role in the treatment of all young women with endometrial cancer considering conservative management [35]. If Lynch/HNPPC syndrome is diagnosed, this will not only have important implications for the patient herself, but it may lead to lifesaving interventions for close family members as well. Appropriate laboratory testing should also be considered before commencing progestin therapy. The exact histologic diagnosis and accurate estimation of the disease extent is essential before deciding to administer fertility-sparing progestin therapy.

Histologic Diagnosis

Dilatation and curettage biopsy (DCBx), office endometrial biopsy, and hysteroscopic biopsy can be performed for the histologic diagnosis of endometrial cancer and grading of...
histologic differentiation of tumor. However, DCBx is the preferred method of histologic diagnosis before commencing fertility-sparing progestin therapy. Office endometrial biopsy is an accurate and convenient diagnostic method that can detect over 90% of endometrial cancers [36, 37]. However, its diagnostic accuracy is limited for small localized tumor [38]. It is very difficult to differentiate grade 1 adenocarcinoma from atypical complex hyperplasia [39] and to accurately determine the histologic grade of tumor using the small tissue samples that are obtained by office endometrial biopsy [40]. The histologic grade of tumor determined by office endometrial biopsy was upgraded after hysterectomy in 26% of cases, whereas the grade determined by DCBx was upgraded in 10% of cases after hysterectomy [40].

DCBx can also provide a therapeutic benefit by removing all, or at least most, of the cancer tissues in the endometrial cavity, whereas office endometrial biopsy serves a diagnostic role only. In a previous study of hysterectomy specimens, there was no residual tumor found in 11% of patients who underwent office endometrial biopsy and in 2% of patients who underwent DCBx [39]. There are two reported cases of successful fertility-sparing management via the therapeutic effects alone of DCBx [41, 42].

Hysteroscopic biopsy is also an accurate diagnostic method for endometrial adenocarcinoma. It provides direct assessment of the extent of the endometrial lesion and an accurate diagnosis when previous methods have been equivocal [43]. Some studies have suggested an increased risk of the peritoneal spread of endometrial cancer during hysteroscopy caused by the use of liquid distention medium [44], although others have not supported this [45, 46]. We thus contend that it would be better to use hysteroscopic evaluation as an adjunct to DCBx in cases with an equivocal diagnosis.

The pitfall in the histologic diagnosis of endometrial cancer and grading of the histologic differentiation of these tumors from biopsy material (regardless of the type of biopsies) without hysterectomy is that the diagnosis, histologic type, and grade can change after hysterectomy. There is also a significant inter- and intraobserver discrepancy of up to 40% in the differentiation between atypical endometrial hyperplasia and well-differentiated adenocarcinoma [47, 48] and in the determination of the histologic grade of tumor [49]. It is reported that the grade of tumor may change in 25% of cases and be upgraded in 10% of cases of endometrial cancer after hysterectomy [40, 50]. In addition, studies have shown that the endometrioid histology may change to other histologic types or other primary cancers after a hysterectomy [51–53].

### Determination of Disease Extent

Before administering fertility-sparing progestin therapy, the extent of disease should be fully determined. The absence of cervical, myometrial, adnexal, lymph node, or peritoneal involvement and also the lack of any distant metastasis should be thoroughly verified. Clinical staging can only be done using imaging, although such clinical staging will be upstaged in up to 13%–22% of cases after surgical staging [54].

In the evaluation of myometrial invasion, contrast enhanced magnetic resonance imaging (MRI) is the preferred method as it has better accuracy compared with transvaginal ultrasonography, computed tomography (CT) and noncontrast enhanced MRI [54–59]. The accuracy of contrast enhanced MRI in the evaluation of cervical invasion, adnexal involvement, and lymph node metastasis has been reported also. The sensitivity and specificity of contrast-enhanced MRI is reported as 75%–80% and 94%–96%, respectively, in detecting myometrial invasion; 75%–80% and 94%–96%, respectively, in detecting cervical invasion; and 50% and 95%, respectively, in detecting lymph node metastasis [60]. This imaging modality can be reasonably used to assess disease extent in endometrial cancer patients.

Recently, the utility of positron emission tomogram (PET) or PET-CT in the detection of lymph node metastases in early-stage endometrial cancer cases has been reported, with a sensitivity and specificity of 63% and 94.7%, respectively [61]. This level of accuracy is comparable to that of contrast enhanced MRI [62], but further evaluations are required to fully validate this.

The risk of adnexal, lymph node, and peritoneal metastasis in low risk endometrial cancer patients with well-differentiated tumors and no myometrial invasion detected by imaging technology is extremely low. Hence, laparoscopic evaluation of the adnexa, lymph node, and peritoneal cavity is not recommended unless imaging studies suggest a suspicious involvement of these regions in tumor spread.

Synchronous ovarian cancer is one of the concerns to consider before initiating fertility-sparing progestin therapy. Some investigators have suggested diagnostic laparoscopy because the incidence of synchronous ovarian cancer ranged between 11% and 29% in their patient series [6, 8, 17, 63–65]. However, most of these were small, single-institution studies. Other studies have suggested a much lower incidence range of 2.2%–6.9% [66–68], and a recent population-based study and additional large multicenter studies have reported an incidence range of approximately 3%–4.5% [69–72]. Hence, the incidence of synchronous ovarian cancer among candidates for fertility-sparing progestin therapy appears to be relatively low, and a diagnostic laparoscopy would not be required unless there was some clinical evidence of an ovarian tumor.

### Preferred Progestins

Oral medroxyprogesterone acetate (MPA) and megestrol acetate (MA) are the most commonly used progestins for fertility-sparing therapy, with approximately 80% of the treated patients receiving continuous daily oral doses of these agents [73–75]. The potency of these two drugs in terms of an endometrial response has been reported to be similar [76, 77]. However, there has been no specific study comparing the efficacy of these two oral agents in fertility-sparing therapy. Although Park et al. [14] suggested that the complete response

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**Table 1.** Optimal indications for fertility-sparing progestin therapy

| 1. Histologically confirmed endometrioid type endometrial adenocarcinoma |
| 2. Well-differentiated tumor |
| 3. Disease confined to the endometrium |
| 4. No evidence of myometrial invasion on imaging study |
| 5. No clinical evidence of extraterine spread of disease |
| 6. Strong desire to preserve fertility |
| 7. Age (≤40 years); relative indication |
| 8. No contraindication for medical treatment |
| 9. Informed consent with the understanding that this is not a standard treatment and carries a higher risk of recurrence |
rate was similar between MPA and MA and that the recurrence rate was lower for MPA-treated cases in their subgroup analysis, further evaluation is required.

Recently, a progestin-containing intrauterine device has been used as a sole agent or in conjunction with oral progestin for fertility-sparing therapy [78]. This device can deliver a higher dose of progestin to the endometrium than orally administered progestin [79] and can avoid systemic complications associated with high doses of oral progestin including thromboembolism, weight gain, mood and libido changes, headaches, breast tenderness, sleep disorders, and leg cramps [50, 51, 80].

Optimal Dose and Duration of Progestin Therapy
The optimal dose of oral MPA and MA for fertility-sparing therapy is not currently well defined. In previous studies, the progestin doses varied from 60 to 1,800 mg/day for MPA and 10 to 400 mg/day for MA [73–75]. The most frequently used dose ranges of MPA and MA were 200-800 and 40-400 mg/day, respectively, with most patients receiving doses of ≳400 and ≲200 mg/day, respectively [73–75]. A high daily dose of oral progestin is typically used in clinical practice, but it is not clear whether low- or high-dose progestin is more effective. In a previous Gynecologic Oncology Group randomized trial of advanced and recurrent endometrial cancer, the response rate and progression-free survival outcome following MPA therapy was higher in low-dose group (200 mg/day) than in high-dose group (1,000 mg/day) [81]. However, this comparison has never been investigated for fertility-sparing therapy in a randomized trial. In a study by Park et al. [14], subgroup analysis of the response rate and recurrence rate in endometrial cancer patients did not differ between low-dose (MPA or MA, <250 mg/day) and high-dose (MPA or MA, >250 mg/day) fertility-sparing treatment groups. Further evaluations are warranted to elucidate the optimal dose of progestin for fertility-sparing therapy.

The median treatment duration to a complete response has differed between studies of progestin-treated endometrial cancer patients. Ramirez et al. [73] report that the median time interval to a complete response in this context is 12 weeks (range, 4–60 weeks). Hence, a treatment period of at least 3 months is required to determine treatment failure. If the patient shows disease progression at this time point, definitive surgical management is warranted. However, if the patient has persistent disease without progression at this time point, further treatment with progestin can be performed as some instances of a complete response after 9–12 months of treatment have been reported [14, 23, 51]. Therefore, although it is not clear when progestin treatment failure should be determined in patients with persistent disease without progression, this therapy can be extended to 9–12 months. In this regard, changes to the progestin dose and type can be considered when the response is incomplete at the first evaluation of treatment response. However, the efficacy of this strategy remains to be fully evaluated.

The total progestin treatment duration varies between 3 and 36 months in previous studies [74, 75]. Chiva et al. [82] have reviewed this issue and reported a median of approximately 6 months. It is not yet clear when progestin therapy should be discontinued in patients who achieve a complete response because this ranges from immediately to several months in different cases. However, the benefit of additional progestin therapy for several months after a complete response was not clear in a previous study [14].

Monitoring of Progestin Therapy
Because the impact of progestins on endometrial cancer cells becomes apparent as early as 10 weeks after the start of treatment [83], and an initial exposure period of at least 12 weeks should be allowed before the response is evaluated [84], a reasonable time point for the first pathologic response evaluation is 3 months after the start of treatment. Subsequently, pathologic responses should be evaluated every 3 months during the progestin treatment course until a complete response is achieved. The treatment response should be assessed by histologic evaluation of the endometrium. As the initial diagnosis, DCBx is the preferred method to evaluate the response to progestin therapy. DCBx was also found to be more accurate than office endometrial biopsy in the evaluation of treatment response for progestin-containing intrauterine devices [85]. Frequent use of a hysteroscopic biopsy of the endometrium may adversely impact on future pregnancy outcomes because of the destruction of the basal layer of the endometrium [86], the subsequent replacement of the endometrial lining with fibrosis [87], and potential thermal injury to the myometrium [88].

Surveillance After Progestin Therapy
Surveillance after successful progestin therapy should include periodic interviews to explore any symptoms, physical examinations, and transvaginal ultrasonography at 3-month intervals. However, periodic pathologic evaluations of the endometrium, using office endometrial biopsy, DCBx, or hysteroscopy, need not be recommended in patients who do not have symptoms or signs of recurrence. Frequent pathologic evaluation of the endometrium may not be effective and may adversely affect pregnancy outcomes by causing intrauterine adhesion or destruction of the basal layer of the endometrium [86]. Hence, endometrial pathologic evaluation is recommended only for patients with symptoms or signs suggesting recurrence.

If the patients wish to conceive after achieving a complete response to progestin, pregnancy trials can be attempted immediately. However, if the patients want to delay pregnancy, maintenance therapy using low-dose cyclic progestin, oral medications, or a progestin-containing intrauterine device can be recommended. Because young women with endometrial cancer often have an excessive unopposed estrogen milieu, elimination of this condition using maintenance therapy would be helpful in preventing either recurrence or de novo endometrial cancer [8, 9]. Park et al. [14] have reported in this regard that maintenance therapy is associated with decreased recurrence.

A prophylactic hysterectomy should be recommended after the completion of family planning because of a high reported rate of disease recurrence [73–75]. The safety of alternative strategies such as the delay of hysterectomy until recurrence has not yet been evaluated.

Oncologic Outcomes After Progestin Therapy
The complete response rate to fertility-sparing therapy is reported to range between 25% and 89% in previous case reports and case series [74, 75]. However, recent review
articles and previous studies report a mean complete response rate ranging from 66.7% to 79.7% [73–75, 78, 82, 89–97]. The most recent meta-analysis, which included 408 patients from 32 studies published between 1983 and 2011, reported a pooled complete response rate of 76.2% (95% confidence interval, 68%–85.3%) [98]. However, various types of fertility-sparing therapy were included in these review articles, and meta-analysis and the indication for fertility-sparing therapy were not limited to stage IA (confined to endometrium), grade 1 endometrioid endometrial cancer. Recently, Park et al. [14] reported the largest series of fertility-sparing therapy cases including only oral progestin therapy and using strict inclusion criteria as shown in Table 1. The complete response rate to progestin therapy was 77.7% in that study [14]. Hence, fertility-sparing progestin therapy is highly effective in stage I (confined to endometrium), grade 1 endometrioid endometrial adenocarcinoma.

Montz et al. [80] have reported for the first time the use of a progestin-containing intrauterine device for stage IA (without myometrial invasion), grade 1 endometrial cancer. However, this was for inoperable cases caused by medical morbidity and not for fertility-sparing therapy [80]. According to a recent review, 17 of 37 patients with stage IA (without myometrial invasion), grade 1 endometrial cancer achieved a complete response with a progestin-containing intrauterine device with a pooled complete response rate of 46% (95% confidence interval, 29%–63%) [78], which is a somewhat disappointing outcome. Hence, some investigators have reported the outcomes of a combined use of progestin-containing intrauterine device with oral progestin [18] or gonadotropin-releasing hormone agonist [17] for fertility-sparing therapy to achieve better outcomes than either agent alone. Kim et al. [18] conducted a prospective observational study of 16 patients with stage IA (confined to endometrium), grade 1 endometrial cancer who were treated with progestin-containing intrauterine device with oral progestin. The results of that study were promising because 14 patients (87%) achieved complete response, and only 2 patients (14.3%) had recurrent disease [18]. Further evaluations are warranted in this regard.

Although the initial response rate of endometrial cancer patients to progestins is very promising, a significant proportion of these cases subsequently show recurrence. According to the findings reported in previous review articles, the endometrial cancer recurrence rate after successful fertility-sparing therapy ranges between 19.2% and 33.8% [73–75, 78, 82, 89–97]. The most contemporary meta-analysis of these patients reported a pooled recurrence rate of 40.6% (95% confidence interval, 33.1%–49.8%) [98]. In the study of Park et al. [14], the recurrence rate after successful progestin therapy was 30.4%, so that the durable complete response rate to progestin therapy was 54.5%. High recurrence rates after fertility-sparing therapy reflect the fact that the goal of this treatment approach is to delay any definitive surgical management to allow child bearing and not to cure the disease. Close surveillance is therefore mandatory after achieving a complete response to progestin treatment.

The safety of fertility-sparing therapy is supported by the findings that subsequent disease progression is extremely rare even in patients who did not respond and that almost all recurrences are well-differentiated tumors confined to the endometrium and are thus still curable with definitive surgical management. In the literature, only 10 patients with stage II or higher disease after fertility-sparing therapy have been reported [98], 4 of whom died of disease [99–102]. However, it is not clear whether these cases had true early endometrial cancer at their initial diagnosis and whether fertility-sparing therapy compromised their survival. Park et al. [14] report that of 148 patients in their series with stage IA (confined to endometrium), grade 1, endometrioid endometrial adenocarcinoma who commenced fertility-sparing progestin therapy, no cases of disease progression over stage IA, grade 1 disease emerged during or after progestin therapy. All cases of treatment failure and recurrent disease in that cohort were successfully salvaged by definitive surgical management or progestin retreatment [14].

**Progestin Therapy for More Advanced Disease**

As indicated in Table 1, the optimal indication for fertility-sparing progestin therapy is stage IA, grade 1 endometrial cancer without myometrial invasion. Sometimes, however, patients with superficial myometrial invasion and/or grade 2–3 disease may want to preserve their fertility. Only a few studies have reported the outcomes of fertility-sparing treatment in patients with stage IA, grade 2–3 disease without myometrial invasion as a part of their wider analyses (Table 2) [19, 51, 103–107]. Recently, Park et al. [12] reported the oncologic and reproductive outcomes in a cohort of endometrial cancer patients with superficial myometrial invasion and/or grade 2–3 disease. The complete response rates to progestin therapy in that study were 76.5%, 73.9%, and 87.5%, respectively, for patients with stage IA (without myometrial invasion), grade 2–3 disease; patients with stage IA (with superficial myometrial invasion), grade 1 disease; and patients with stage IA (with superficial myometrial invasion), grade 2–3 disease [12]. The recurrence rates after progestin therapy in that study were 23.1%, 47.1%, and 71.4%, respectively, with no evidence of disease progression after fertility-sparing progestin therapy [12]. Fertility-sparing progestin therapy is therefore a viable treatment option in patients with stage IA (without myometrial invasion), grade 2–3 disease and in patients with stage IA (with superficial myometrial invasion), grade 1 disease. However, further evaluations are still required before recommending fertility-sparing progestin therapy to endometrial cancer patients with more advanced disease in routine practice.

**Progestin Therapy for Recurrent Disease**

Most endometrial cancer patients who have recurrent disease undergo definitive surgical management including hysterectomy. If these patients have not had a successful pregnancy at the time of recurrence, they may still want to preserve their fertility. Because most recurrent disease in endometrial cancer cases involves well-differentiated tumors confined to the endometrium, a second round of fertility-sparing progestin therapy can be considered. However, the treatment outcomes are not well known in such cases, and few studies have addressed this as a part of their wider analyses (Table 3) [19, 102, 108–110]. The complete response rate to progestin retreatment is reported to range from 52% to 100% for recurrent disease. Recently, Park et al. [13] reported their
findings for the largest endometrial cancer series yet analyzed regarding this subject. Of 33 patients with recurrent endometrial cancer in that study who received a second round of fertility-sparing progestin therapy, a complete response rate of 89% and recurrence rate of 42% were recorded, with no disease progression [13]. These outcomes were similar to those of the primary fertility-sparing progestin therapy. Again, progestin retreatment in patients with recurrent disease can therefore be considered a safe and effective intervention for patients who still want to preserve their fertility.

### Pregnancy Outcomes After Progestin Therapy

The pregnancy outcomes after fertility-sparing progestin therapy are not well known because most previous studies were case reports or involved small case series and mostly focused on the oncologic safety of the treatment rather than pregnancy outcomes. In a previous meta-analysis that included 325 women from 26 studies, 75 women achieved at least 1 live birth, with a pooled live birth rate of 28% (95% confidence interval, 21.6%–36.3%) [98]. However, the live birth rate would be higher than this if only women who tried to conceive after successful fertility-sparing therapy were considered. Park et al. [111] reported the largest series to be evaluated in terms of pregnancy outcome after progestin therapy in women with stage IA (confined to endometrium), grade 1 endometrioid endometrial adenocarcinoma. In that study, of the 144 patients who achieved complete remission, 70 patients attempted to conceive, 51 patients achieved at least 1 pregnancy, and 46 patients gave birth to a healthy child [111]. The pregnancy rate was therefore 73%, and live birth rate was 66% when considering only women who tried to conceive [111]. In that study, the spontaneous abortion rate was slightly higher than and the ectopic pregnancy and preterm delivery rates were similar to those of general population [111].

Because anovulatory disorders including polycystic ovary syndrome are a frequent predisposing factor for endometrial adenocarcinoma in young women, the incidence of subfertility or infertility is higher in these women than in the general population [8, 9, 111]. Therefore, assisted reproductive technologies are often required in these cases to achieve pregnancy [98, 111]. The pregnancy rate and live birth rate were found to be significantly higher in women who received assisted reproductive technology than in women who attempted natural pregnancy [98, 111]. The use of fertility drugs during assisted reproductive technologies increases estrogen production [112]. However, it is controversial as to whether this would increase the risk of recurrence after fertility-sparing progestin therapy for early endometrial cancer [113–116]. Park et al. [111] assessed the association between the use of fertility drugs and an increased risk of recurrence after successful progestin therapy but did not find any such association. Instead, these authors found that patients who

### Table 2. Published studies showing the efficacy of progestin therapy in endometrial cancer with myometrial invasion and/or grade 2–3 differentiation

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number of cases</th>
<th>Progestin therapy</th>
<th>Complete response, n (%)</th>
<th>Recurrence, n (%)</th>
<th>Follow-up time, median or range, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sardi et al. [103]</td>
<td>1998</td>
<td>1</td>
<td>MPA (50 mg/day)</td>
<td>0</td>
<td>0</td>
<td>20</td>
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<td>Zuckerman et al. [104]</td>
<td>1998</td>
<td>1</td>
<td>MPA</td>
<td>1 (100)</td>
<td>0</td>
<td>Not reported</td>
</tr>
<tr>
<td>Imai et al. [105]</td>
<td>2001</td>
<td>2</td>
<td>MPA (600 mg/day)</td>
<td>1 (50)</td>
<td>1 (100)</td>
<td>7–47</td>
</tr>
<tr>
<td>Kaku et al. [51]</td>
<td>2001</td>
<td>2</td>
<td>MPA (600 or 800 mg/day)</td>
<td>1 (50)</td>
<td>0</td>
<td>19–22</td>
</tr>
<tr>
<td>Gottlieb et al. [19]</td>
<td>2003</td>
<td>3</td>
<td>MPA (200 or 600 mg/day) or MA (160 mg/day)</td>
<td>3 (100)</td>
<td>1 (33)</td>
<td>16–94</td>
</tr>
<tr>
<td>Koskas et al. [106]</td>
<td>2011</td>
<td>3</td>
<td>NES (20 mg/day), MA (160 mg/day), or NG (5 mg/day)</td>
<td>3 (100)</td>
<td>2 (67)</td>
<td>12–60</td>
</tr>
<tr>
<td>Brown et al. [107]</td>
<td>2012</td>
<td>1</td>
<td>LNG-IUD</td>
<td>1 (100)</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Park et al. [12]</td>
<td>2013</td>
<td>48</td>
<td>MPA (80–1,000 mg/day) or MA (40–240 mg/day)</td>
<td>37 (77)</td>
<td>16 (43)</td>
<td>48</td>
</tr>
</tbody>
</table>

Abbreviations: MPA, medroxyprogesterone acetate; NES, norethisterone; NG, nomegestrol.

### Table 3. Published studies showing the efficacy of progestin therapy for recurrent endometrial cancer

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Number of cases</th>
<th>Progestin therapy</th>
<th>Complete response, n (%)</th>
<th>Recurrence, n (%)</th>
<th>Median follow-up time, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gottlieb et al. [17]</td>
<td>2003</td>
<td>4</td>
<td>MA (160 or 320 mg/day)</td>
<td>4 (100)</td>
<td>0</td>
<td>40</td>
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<tr>
<td>Ushijima et al. [99]</td>
<td>2007</td>
<td>8</td>
<td>MPA (600 mg/day)</td>
<td>6 (75)</td>
<td>5 (83)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Yu et al. [107]</td>
<td>2009</td>
<td>2</td>
<td>Not specified</td>
<td>1 (50)</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Eftekhar et al. [105]</td>
<td>2009</td>
<td>3</td>
<td>MA (320 mg/day)</td>
<td>2 (67)</td>
<td>0</td>
<td>Not reported</td>
</tr>
<tr>
<td>Perri et al. [106]</td>
<td>2011</td>
<td>11</td>
<td>Not specified</td>
<td>11 (100)</td>
<td>5 (45)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Park et al. [13]</td>
<td>2013</td>
<td>45</td>
<td>MPA (80–500 mg/day) or MA (80–160 mg/day)</td>
<td>28 (85)</td>
<td>15 (18)</td>
<td>51</td>
</tr>
</tbody>
</table>

Abbreviations: MA, megestrol acetate; MPA, medroxyprogesterone acetate.
achieved at least one pregnancy had a lower risk of disease recurrence regardless of the use of fertility drugs [111]. Fertility drugs can therefore be used safely after successful fertility-sparing progestin therapy, and a history of subfertility or infertility should not be a contraindication for such therapy.

Because anovulatory disorders including polycystic ovary syndrome are a frequent predisposing factor for endometrial adenocarcinoma in young women, the incidence of subfertility or infertility is higher in these women than in the general population. Therefore, assisted reproductive technologies are often required in these cases to achieve pregnancy.

**CONCLUSION**

Fertility-sparing progestin therapy is highly effective in selected young women with primary and recurrent endometrial cancer. The selection of appropriate patients through comprehensive pretreatment evaluations is of paramount importance to achieve the best outcomes without compromising survival outcomes. Because of the high rate of recurrence after successful fertility-sparing management, close surveillance is mandatory, and prophylactic hysterectomy is the best option after a successful pregnancy. Pregnancy outcomes are very promising in these cases with the aid of assisted reproductive technologies. Continuous daily oral MPA are MA are the preferred progestins for fertility-sparing therapy. However, future studies should be performed to determine the optimal dose and treatment duration of these agents.

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